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FERROUS SULFATE POISONING

REPORT OF THREE CASES

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DURING the last four years there has been an increasing awareness by the profession of the toxicity of ferrous sulfate, one of the most frequently prescribed drugs in the medical armamentarium. Interest in this problem was initiated by the excellent article by Forbes[1] in 1947. Subsequent reports by Thomson,[2] Foucar and associates,[3] Smith and collaborators,[4] and others[5, 6, 7] have served to focus the attention of physicians, particularly in the field of pediatrics, on the lethal properties of what was once considered a completely innocuous drug.

The following are three case reports of ferrous sulfate intoxication observed during the past year, one of which ended fatally in less than five hours after ingestion of the drug.

CASE REPORTS

CASE 1.—D. M., a 15-month-old white girl, was admitted to the Dependents' Service of the U. S. Naval Hospital, Great Lakes, Ill., at 11:00 P.M. on March 7, 1951, after having ingested between fifteen and twenty 5 gr. (0.3 Gm.) tablets of ferrous sulfate six hours previously. About fifteen minutes after eating the tablets she began to vomit. The emesis consisted of incompletely digested tablets and brown mucoid material. The vomiting continued every few minutes and was either pure retching or productive of the material mentioned above. Upon arrival at the hospital she was pale, cold, clammy, and somewhat listless.

Physical examination on admission to the hospital revealed a temperature of 98.6° F. rectally, a pulse of 140 beats per minute, respirations 32 per minute, and a blood pressure of 86/50. She was well developed and well-nourished, but appeared lethargic, pale, and was rather slow to respond to ordinary stimuli. Save for slight abdominal distention, and a dry tongue, the general physical examination was normal. The deep tendon reflexes were depressed, but otherwise the neurological examination was normal.

The routine urine was normal. The hemoglobin was 12.5 grams, the red blood cell count 4,870,000, and the white blood count 7,350 per cubic millimeter, consisting of 42 per cent neutrophils, 52 per cent lymphocytes, 4 per cent monocytes, and 2 per cent eosinophils.

She was given 600 c.c. of 5 per cent dextrose in water intravenously, and during the first twenty-four hours af-

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ter admission she had three to four semiliquid, foul-smelling stools, varying in color from green to black.

Vomiting occurred only once and this was shortly after admission. This emesis was greenish and contained bright red and brownish flecks of blood. The blood pressure fluctuated from 70 to 90 systolic, and 40 to 60 diastolic. Twelve hours after the ferrous sulfate ingestion the girl was alert, cooperative, and taking and retaining liquids well.

Forty-eight hours after admission she was eating a full diet and was discharged asymptomatic.

CASE 2.—J. B., an 18-month-old white male infant, was admitted to the Dependents' Service of the U. S. Naval Hospital, Great Lakes, Ill., at 8:45 A.M. on May 21, 1951, after having ingested fifteen enteric, chocolate-coated 5 gr. (0.3 Gm.) ferrous sulfate tablets one hour and forty-five minutes previously.

He showed no ill effects from the tablets until 8:00 A.M., one hour after the ingestion, when he suddenly vomited and seemed to turn blue around the lips. On the way to the hospital he "fell asleep," and upon arrival, forty-five minutes later, could not be aroused.

The admission physical examination showed a well-developed and well-nourished 18-month-old boy who was extremely pale. His clothes were streaked with chocolate, and particles of the tablets could be found between his teeth and in the vomitus. He was having almost continuous clear, watery, foul-smelling stools. The respirations were 16 per minute, apical heart rate 132 beats per minute, and the blood pressure 80/60 with a thready, almost imperceptible pulse. The pupils were dilated, but the funduscopic examination was normal. There was marked hypotonia and hyporeflexia. He could be aroused slightly by painful stimuli.

The routine urine examination was normal. The hemoglobin was 10 grams, the red blood cell count 4,460,000, and the white blood cell count was 21,700, consisting of 56 per cent neutrophils, 38 per cent lymphocytes, and 6 per cent monocytes.

The stomach was lavaged with normal saline, with the recovery of brownish particles in the aspirated fluid. One ferrous sulfate tablet was vomited. A cross match was drawn and he was then given 150 c.c. of whole plasma intravenously by closed infusion, as well as 125 c.c. of 5 per cent dextrose in water, followed by 50 c.c. of normal saline, 200 c.c. of whole blood, 275 c.c. of normal saline, 200 c.c. of whole plasma, and 250 c.c. of 5 per cent dextrose in water at 20 drops per minute to make a total of 1,250 c.c. of intravenous fluids in the first twenty-four hours.

Following the first plasma infusion, the boy improved and the pulse became stronger, although he remained unresponsive until four and one-half hours after the ingestion, when he finally could be aroused. However, for the next twenty-four hours he was very lethargic and drowsy. The watery, clear stools continued for sixteen hours when they became black and tarry, having much the appearance of meconium. These persisted at a frequency of two to four stools each day until the infant was discharged from the hospital. He vomited about ten to twelve times in the first twenty hours; each time the emesis contained the offered fluids and some pink or brown, bloody material.

By the morning after admission he was retaining liquids well, and vomited but once more during his hospital stay. His temperature which had been normal on admission rose to 101° F. (rectally), eighteen hours later, but otherwise no temperature elevation was present during the convalescence.

He was given prophylactic procaine penicillin, 300,000 units intramuscularly each day, and the lung fields remained clear to auscultation, save for a few sonorous rhonchi at the time of the temperature elevation.

Forty-eight hours after ingestion of the ferrous sulfate, the boy was up and about the ward. The white blood cell count was 14,600 with essentially the same differential percentages as on admission. The hemoglobin and red blood cell count remained the same, despite the gastrointestinal blood loss, which probably can be explained on the basis of the 200 c.c. whole blood transfusion.

Although the patient was still having tarry stools on May 26, 1951, five days after the ferrous sulfate ingestion, he was discharged home. A follow-up examination two weeks later failed to reveal any complications or sequelae, and the stools had reverted to normal color and consistency within two days after discharge.

CASE 3.—L. C., a white female aged 26 months, was admitted on Sept. 24, 1950, two and one-half hours after having swallowed an unknown quantity of chocolate-coated tablets which her mother had been taking to prevent an anemia of pregnancy. These tablets were later identified as ferrous sulfate. About ten minutes after the ingestion, the child began to vomit and continued to do so up to the time of admission. One and one-half hours after taking the tablets she was seen by a physician who described her condition as being limp and lethargic. The child was transferred to the Dependents' Service of the U. S. Naval Hospital, Great Lakes, Ill., via ambulance without any prior treatment having been given.

The child was lethargic and unresponsive on admission. She was breathing stertorously and there was a mottled cyanosis of the lower extremities and of the hands. The pulse and blood pressure were unobtainable. The heart sounds were weak with a rate of 148 beats per minute. There was a sweetish odor on the breath, and the teeth, gums, and buccal mucosa were coated with particles of the ingested material. A marked hypotonia was present. There was absence of the superficial, as well as the deep tendon reflexes.

The treatment consisted of external heat, oxygen, gastric lavage, infusion of 2.5 per cent dextrose in saline, and caffeine stimulation. The child appeared to rally briefly after which there was progressive deterioration with death occurring about two hours after admission, approximately four and one-half hours after the ferrous sulfate ingestion.

Following investigation of the circumstances of the patient's death, it was estimated that the child had ingested about thirty to forty tablets, each of which contained 5 gr. (0.3 Gm.) of ferrous sulfate.

Autopsy findings:* Save for some white, frothy material in the larynx, lower trachea and larger bronchi, and minimal posterior, basilar atelectasis in both lungs, the gross pathological findings were confined to the gastrointestinal tract. The esophagus showed no lesions, but the stomach was slightly distended and contained 30 c.c. of brownish, blood-stained material with some white flecks. The entire mucosa was hemorrhagic and edematous (Fig. 1). Many areas, particularly at the summit of the folds, showed blackish discoloration with multiple shallow erosions. After formalin fixation the mucosa took on a brownish hue. This reaction stopped abruptly at the pylorus. The small intestine contained blackish material resembling meconium, but the mucosa showed no gross abnormalities. The large intestine was also normal.

Chemical analysis of the stomach and small intestinal contents gave a positive Prussian blue reaction. The same test performed on one of the vomited pills and on a chocolate, enteric-coated tablet from the box of pills which the patient's mother had been taking to help prevent an anemia of pregnancy, also gave positive reactions.

*The post-mortem examination was carried out by Commander R. H. Fuller (MC) United States Navy.

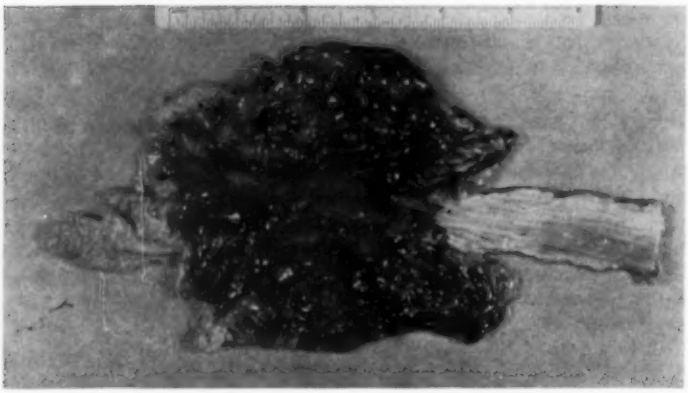

Fig. 1.—Photograph of stomach, showing hemorrhagic, edematous gastric mucosa ending abruptly at the pylorus. Many areas showed blackish discoloration.

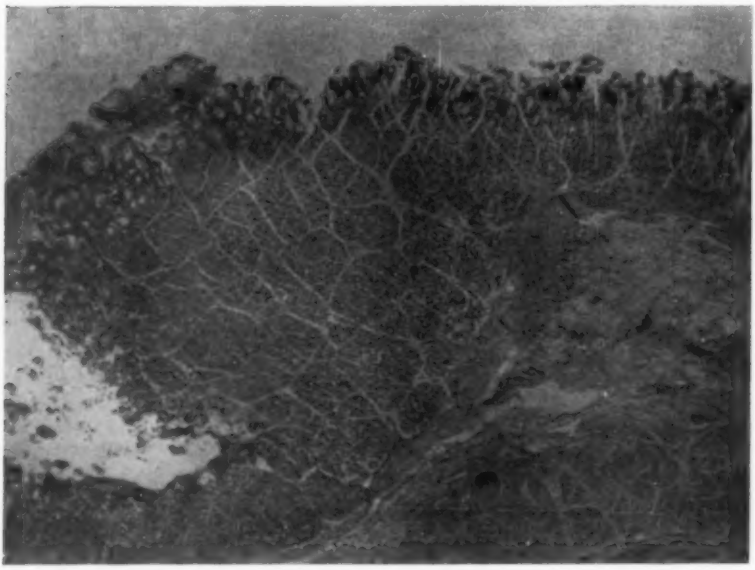

Fig. 2.—Photomicrograph of stomach, showing superficial necrosis of mucosa as well as hemorrhage and early inflammatory reaction.

Microscopically the cytoplasm of the hepatic cells was somewhat swollen and hydropic, but no necrosis was present. The lungs showed vascular stasis, and patchy basilar atelectasis. Histological examination of the stomach revealed the superficial one-third of the mucosa to be necrotic and discolored greenish-brown (Fig. 2). There was hemorrhage into the mucosa with a very early inflammatory reaction. The reticular fibers of the mucosa were crusted with greenish-brown material which resembled the ferruginization seen frequently in old infarcts. The brain both grossly and microscopically was normal. The final pathological diagnosis was poisoning, acute, due to ferrous sulfate.

DISCUSSION AND CONCLUSIONS

The dominant symptoms and signs of acute ferrous sulfate intoxication are well exemplified in these three cases. The vomiting with retching, the clear, watery stools later becoming tarry, the profound shocklike picture and collapse, with rapid, weak, or imperceptible pulse and low blood pressure, the hypotonia, the hyporeflexia, the dilated pupils, and the semicomatose or comatose state were all present as reported formerly by Forbes[1] and Smith and associates.[4] Forbes' two patients expired thirty and fifty-three hours after ferrous sulfate ingestion, while the fatal case presented above, the case of Smith and co-workers,[4] and the case of Foucar and collaborators[3] all died within twelve hours of ingestion.

It must again be emphasized to the medical profession that ferrous sulfate intoxication is a reality. When the latter does occur, immediate treatment of the peripheral vascular collapse with plasma and/or whole blood is imperative.

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FERROUS SULFATE POISONING

Report of a Fatal Case

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SEVERE toxic complications and death due to overdosage with ferrous sulfate are considered to be rare. There have been only two fatal cases reported in the American literature,[1, 2] and five deaths have been reviewed in the English literature.[3, 4, 5] The exact mechanism of death is not well understood, but the clinical course and pathological findings have been very similar in all cases. In general, these cases of fatal poisoning presented initially the picture of severe gastroenteritis accompanied by marked shock and acidosis. In most instances this stage of the illness responded favorably to gastric lavage, blood transfusions, and general supportive therapy. Death usually occurred between twenty-four and forty-eight hours after the onset, with the appearance of a secondary toxic state manifested by signs of pneumonia and hyperpyrexia. Post-mortem findings have been hemorrhage and necrosis in the stomach and small intestine, degenerative changes in the liver, a hemorrhagic bronchopneumonia, and evidence of widespread bleeding. Smith, Jones, and Cochran[1] have made a recent report in the American literature with a comprehensive discussion of the possible causes of death. It is of interest to note that they felt that methemoglobinemia played a prominent part as the cause of death. It is also mentioned in their article that a delayed blood-clotting mechanism may be of importance.

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CASE REPORT

R. D., a 19-month-old Caucasian male, was admitted to the Los Angeles County Hospital at 1:00 P.M. on May 15, 1951. He was reported to have ingested an undetermined number of 0.2 Gm. (3 gr.) enteric-coated ferrous sulfate tablets at 9:00 A.M. that morning. Within thirty minutes he had begun to vomit. Lavage was done at an emergency hospital at about 11:00 A.M. and two partly dissolved tablets were recovered. Shortly after this the child became lethargic and developed a diarrhea with red liquid stools. He was then brought to this hospital. Physical examination revealed a well-developed 19-month-old child who was cyanotic, had rapid shallow respirations, and a very weak pulse. The abdomen was generally tender with hyperactive peristalsis. The child was lethargic, but did respond well to painful stimuli. The laboratory data showed a hemoglobin of 18.0 grams and a white blood count of 37,800. The urine contained albumin and gave a positive benzidine test, but no red cells were seen on microscopic examination. The carbon dioxide combining power was 15 meq. per liter and the nonprotein nitrogen was 46 mg. per cent. Methemoglobin was less than 5 per cent of the total hemoglobin. The stool was red and watery and contained fragments which grossly appeared to be the ingested

tablets. The treatment consisted of intravenous fluids, blood transfusion, one dose of BAL, penicillin, streptomycin, and oxygen. The patient was clinically out of shock in four hours. Seven hours after admission the temperature rose to 103° F. and the patient again appeared to be in shock. He was given 35 mg. of vitamin K and transfused again. On the following day the diarrhea began to subside and the patient appeared well hydrated and was voiding normally. Bleeding time was found to be four minutes. Intravenous fluids were continued to maintain hydration and electrolyte balance, and only Amphojel and small sips of water were given by mouth. At 10:00 P.M. on the second hospital day the temperature suddenly rose to 104° F. and the patient had a transitory episode of convulsive movements. Cooling measures were instituted. A few hours later the child was noted to have rapid shallow breathing and signs of bronchopneumonia became prominent. The child expired suddenly forty hours after the ingestion of the ferrous sulfate.

The essential autopsy findings were as follows: The body was that of a white male infant, 72 cm. in length and weighing 10.6 kilograms. There was slight icterus of the skin and sclerae.

The lungs were highly edematous, congested, and hemorrhagic. There was hemorrhage beneath both the parietal and visceral pleura. This hemorrhage was thin and filmlike. There was also some hemorrhage in the parenchyma of the lung, and in the thymus gland. The heart showed no abnormality.

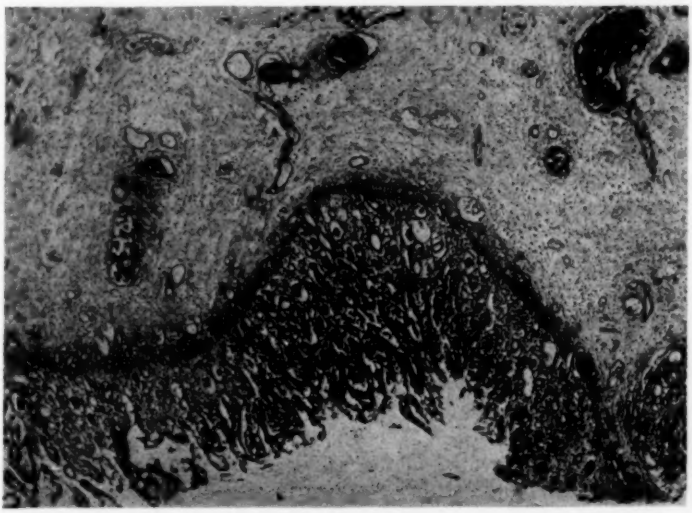

Fig. 1.—Photomicrograph of the small intestine. Area of gangrene stained by the Turnbull blue method showing necrosis of the mucosa. Note that some of the submucosal blood vessels contain thrombi, while others contain iron granules. (×75.)

A small amount of cloudy fluid was present in the abdomen. The liver was large, flabby, and of yellow-tan color. On cross section, it was somewhat mottled and showed varying shades of red to tan. The esophagus and stomach were not corroded. There was a small amount of blackish material, probably altered blood, in the stomach. There were four areas of gangrene in the small bowel. The first of these appeared in the lower jejunum and was 15 cm. in length. The bowel wall was purple in color,

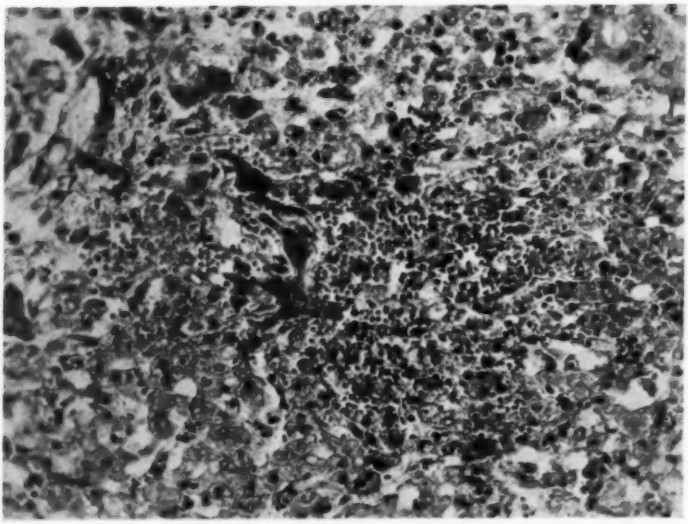

Fig. 2.—Photomicrograph of the liver, showing the central necrosis and hemorrhage. (Hematoxylin and eosin stain ×220.)

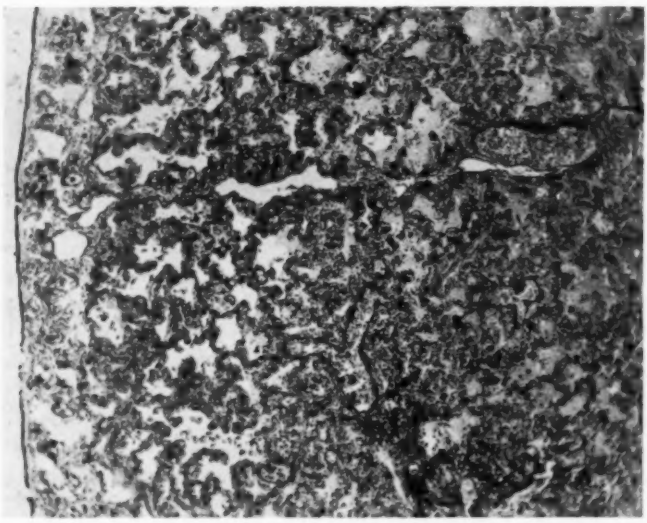

Fig. 3.—Photomicrograph of the lung, showing the edema fluid in the alveoli. (Hematoxylin and eosin stain, ×65.)

the mucosa was sloughed, and there was blackish material in the lumen. The next three areas of gangrene occurred in the ileum and measured 8, 2, and 6 cm. in length. The intervening small bowel was only mildly congested. There were large masses in the mesentery serving the gangrenous areas. These were aggregated lymph nodes which were not densely adherent. The largest node was about 1.5 by 1.0 cm. The cut surfaces were pink and granular and more or less uniform in appearance. The other abdominal organs showed no abnormality.

The kidneys were slightly swollen. The spleen was of normal size and the cut surface appeared normal. There was no gross abnormality of the brain or its coverings.

Microscopic examination of sections stained by routine hematoxylin and eosin method showed necrosis of the mucosa of the small intestine. There was a large amount of hemorrhage present throughout the muscular coats, beneath the serosa, and in the submucosa. Thrombosis of small blood vessels in the bowel wall was noted (Fig. 1). The lymph nodes showed hyperplasia without definite characteristics. In the liver there was a central degeneration. The central liver cells stained very poorly and there was considerable hemorrhage present (Fig. 2). Proliferation of the bile capillaries was noted. In sections stained for iron, using the Turnbull blue reaction, there was a coating of iron-containing material in the mucosa of the intestine. In the veins from this area there were numerous large macrophages which contained an abundant amount of iron. The walls of the blood vessels appeared to be stained in many portions. The thrombi were more or less fibrinous in character. Iron was demonstrated in the sinusoids of the adjacent lymph nodes and was present chiefly in macrophages and in some of the littoral cells. No definite accumulations of iron could be demonstrated in the liver or in the other organs. The lungs showed marked congestion and areas of hemorrhage with accumulations of edema fluid (Fig. 3). No consolidation was present. The other organs showed no pertinent abnormalities.

Quantitative iron studies were done on the liver and kidney tissues. The liver contained 6.6 mg. of iron per 100 mg. of tissue, and the kidneys contained 4.0 mg. of iron per 100 mg. of tissue. These values are within normal limits.

DISCUSSION

The action of iron here was localized in segments of the small intestine. The localization was apparently due to the enteric coating of the tablets and subsequent lodging of groups of the ingested tablets in certain areas of the intestine. In these areas there occurred necrosis of the mucosa with uptake of the iron into the blood vessels, resulting in a vascular thrombosis. The thrombosis involved the small vessels and not the large vessels of the mesentery. Apparently the ingested iron reached no farther than the regional lymph nodes, as it could not be demonstrated beyond this point. The degenerative changes in the liver could not be explained as a direct result of iron. They were probably secondary to the toxic effect of the pregangrenous bowel. The hemorrhagic tendency noted in the visceral and parietal pleurae and in the lung is probably a result of liver damage.

It is concluded that the toxic effects of iron are due to high concentrations in the bowel, producing mucosal necrosis which destroys the barrier to iron normally present in the mucosal epithelium. Essentially unaltered iron salts gain entry to veins and lymphatics, producing thrombosis and gangrene. There is no evidence of a systemic effect from absorbed iron per se,

but extensive liver damage and visceral hemorrhage may result from the toxemia produced by this thrombosis and gangrene.

We do not feel that methemoglobinemia played any part as a cause of death, since normal values were obtained at the only time our patient showed cyanosis. We would like to emphasize the biphasic clinical course of initial shock, an intermediate period of relative recovery, then sudden death.

Recent investigators are suggesting that higher therapeutic dosages of ferrous sulfate be used in the treatment of deficiency anemias. It is well known that small dosages will frequently cause gastroenteritis of a mild nature and it is quite probable that sublethal doses may produce some of the pathology described here.

SUMMARY

A case of fatal ferrous sulfate poisoning is reported with a discussion of the clinical and pathological findings.

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THE LIPOPROTEINS OF SERUM IN INFANCY AND CHILDHOOD

I. Lipoproteins in Normal Children

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ALTHOUGH atherosclerosis per se is relatively uncommon in childhood, a study during the early years of life of some of the factors which seem to operate in producing the disease at a later age may aid our understanding of the physiological processes and provide a key to possible prevention of the disease. It has long been suspected that the blood lipids might in some way be related to the pathogenesis of human atherosclerosis. All the major blood lipid constituents, including cholesterol and its esters, phospholipids, and neutral fats have been investigated. These substances are building blocks of a number of giant molecules present in the blood. Gofman and associates[1] have carried out studies based on the premise that a defect could exist in certain of these giant molecules, which would be responsible for the development of atherosclerosis, although the mere analytical levels of any of the above-mentioned building blocks, such as the cholesterol level of the serum, might be of little or no significance.

Recently a class of lipoprotein molecules in the serum of the human being has been demonstrated, which is present with a much higher frequency at high concentrations in patients who have atherosclerosis (those who have survived a myocardial infarction) than in corresponding individuals without known vascular disease.[1, 2, 3] These molecules also were present with increased concentration in other diseases associated with atherosclerosis (diabetes mellitus, the nephrotic syndrome, hypothyroidism, and coronary insufficiency).

The present study deals with a group of 147 normal children, ranging in age from birth to 15 years, in whom the levels of certain lipoproteins in the blood were determined. These normals serve as control data for comparison with the levels found in a group of children with various diseases. Determinations of a certain range of molecules (S_f 10-20) have been made because of previously shown association of these molecules with atherosclerosis.

PROCEDURE

The various lipid constituents of the serum are usually expressed only in terms of total cholesterol, cholesterol ester, etc. From this one cannot predict how the various constituents are distributed among the numerous macromolecules that may exist in serum. These macromolecules, whose molecular weight is up to several millions, contain cholesterol or cholesterol ester along with phospholipids, protein, and neutral fats which serve as their building blocks. It is for the

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detection, on a quantitative basis of these individual macromolecules, that the ultracentrifuge is especially useful.

The ultracentrifuge is a device which was designed for the production of forces many thousands to many million times the force of gravity. Under the influence of such intense gravitational fields of force, individual molecules of the size of protein can be made to undergo sedimentation (if they are more dense than the solution in which they are present) or to undergo flotation (if they are less dense than the solution in which they are present). In either event, if the centrifugal force is sufficiently great to impart an appreciable migration rate to the molecules, a boundary becomes established between the solution containing the large molecules and the region of solution out of which these molecules have migrated. A variety of optical techniques, known as refractive index gradient methods, have been devised for rendering this boundary observable and for measuring the rate of movement of the boundary region itself, as the centrifuge rotor spins.

The rate of movement (sedimentation or flotation) of dissolved molecules in an ultracentrifugal field depends primarily upon size, shape, and density of the molecule and the density and viscosity of the medium in which it is present. A minimum of ten distinct species of lipoproteins may be found in human serum, differing from one another physically in density of the molecule and in ultracentrifugal flotation rates, has been described.[4] Broadly, the lipoproteins may be segregated into major groups, the so-called "low density lipoproteins" (density less than 1.063) and the "high density lipoproteins" (density greater than 1.063). In this study attention will be confined to flotation of the low-density group of molecules.

As a preliminary operation in the study of sera for these molecules a separation is made in the preparative ultracentrifuge. In this process a density increment is given the serum sample by dilution with a concentrated sodium chloride solution. Ultracentrifugation of this serum solution for thirteen hours results in the flotation to the top of the preparation tube of all lipoprotein molecules less dense than the solution. Also during the ultracentrifugation all large molecules of density greater than the solution undergo sedimentation. Thus, after a critical time of ultracentrifugation the low-density group of lipoproteins will have collected as a layer at the top of the preparative tube and all the proteins and dense lipoproteins will have sedimented out of the top portion of the preparative tube. After the centrifuge stops, removal of the top fraction containing the layered low-density lipoproteins can be effected using a capillary pipette. Next the isolated low-density lipoproteins (the top fraction) are studied in the analytical ultracentrifuge. Here the lipoprotein molecules are characterized and identified by their flotation rates. Flotation rates are given in S_f units (Svedbergs of flotation) under the specified conditions.* Thus, a molecule described as having a flotation rate of 20 S units will be referred to

*1 S_f unit = flotation rate of 1 x 10^{-13} cm./sec./dyne./Gm. The specified conditions for these studies refer to use of a sodium chloride solution of density 1.063 Gm. per cubic centimeter at 26° C. If runs are performed under any other conditions, appropriate corrections must be made. Spinco Model L and Model E ultracentrifuges were used throughout.

as a molecule of the 20 S_f class, etc. Usually the samples are centrifuged at 52,640 r.p.m. (forces approximately 200,000 to 250,000 × gravity) for less than one hour, with a series of photographs being taken at various stages of the flotation.

A special optical system allows the moving boundaries of macromolecules to be observed and recorded while the centrifuge is in operation. The basis for detection of these boundaries is the abrupt change in refractive index from the region of solution containing the particular class of large molecules to the region out of which these molecules have migrated. The optical system records such a refractive index change as an inverted peak for floating boundaries, the area over the peak providing a measure of the concentration of these molecules. Thus, the concentration and flotation rates of the large molecules present in a solution can be determined.

The low-density group of lipoproteins found in a given human serum may comprise one or more species of components, differing one from another in size, density, and chemical composition. The individual components may have flotation rates so close together as to be resolvable with difficulty. A typical flotation pattern illustrates the nature of the problem (Fig. 1). Knowing the type of components which exists, it is possible to resolve such a pattern into its individual constituents (Fig. 2).

Details of the ultracentrifugal method have been reported by Gofman and collaborators.[2]

In human serum, the following classes of lipoprotein molecules have been identified:

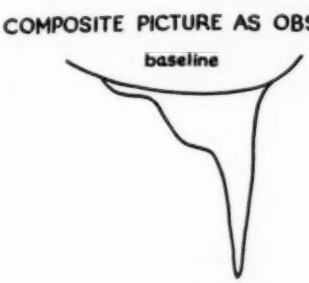

Fig. 1.

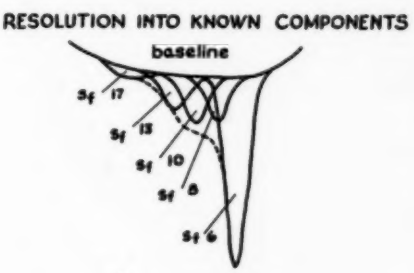

Fig. 2.

Fig. 1.—Diagram illustrating a typical flotation pattern observed in the ultracentrifugal analysis of the low-density lipoproteins of human serum.

Fig. 2.—Resolution of Fig. 1 into the lipoprotein components known to exist in human serum.

(a) Species which migrate with S_f values greater than 75 S_f units. These include the well-known chylomicrons and aggregates of much smaller dimensions than the chylomicrons. The concentration of species in this entire class is increased following fat-containing meals and hence represents part of the acute alimentary lipemia. No independent correlation has been found between components of S_f greater than 75 units and presence of atherosclerosis in human beings.

(b) Species which migrate with S_f values between 30 and 70 S_f units. These species constitute the major

fraction of acute alimentary lipemia and are greatly modified in concentration with relationship to meals.

(c) Species of discrete classes which migrate with rates between 10 and 20 S_f units. These components, whose molecular weights are in the neighborhood of three million, appear definitely related to the presence of atherosclerosis in human beings. The S_f 10-20 molecules are important cholesterol phospholipid and protein-containing substances. This set of components carrying a major fraction of the serum cholesterol is present in every one of some 4,000 samples from adults previously studied—at concentrations varying from individual to individual, but at an essentially constant level for a given individual from time to time.

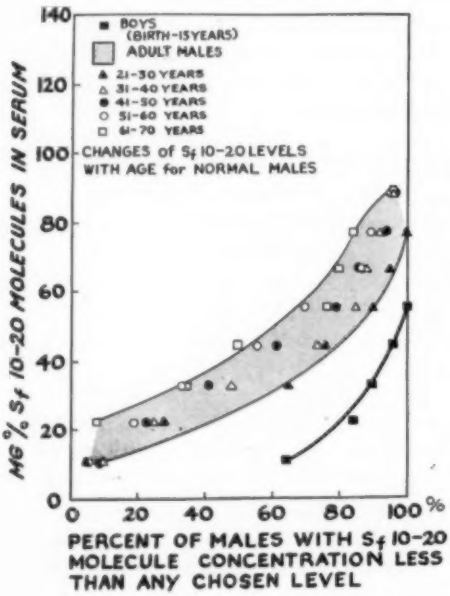

Fig. 3.

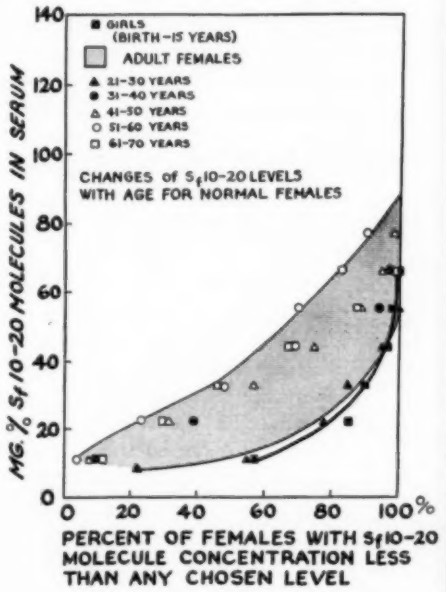

Fig. 4.

Fig. 3.—The level of S_f 10-20 molecules in the serum of male children (solid line) and adult males (shaded area). The values obtained for the boys were significantly lower than those for the men.

Fig. 4.—The level of S_f 10-10 molecules in the serum of female children (solid line) and adult females (shaded area). The levels for the girls approximate those of women between 21 and 30 years of age, but are significantly lower than those of women in the older age groups.

class contains at least three separate species of molecules, each approximately 30 per cent cholesterol by weight, all of which appear to be of significance with respect to atherosclerosis.

(d) Species which migrate with S_f rates between 3 to 8 S_f units. These This set of components does not of itself appear to be related to atherosclerosis.

RESULTS

Measurements of the concentration of S_f 10-20 lipoprotein molecules were performed on the sera of 147 normal children ranging in age from

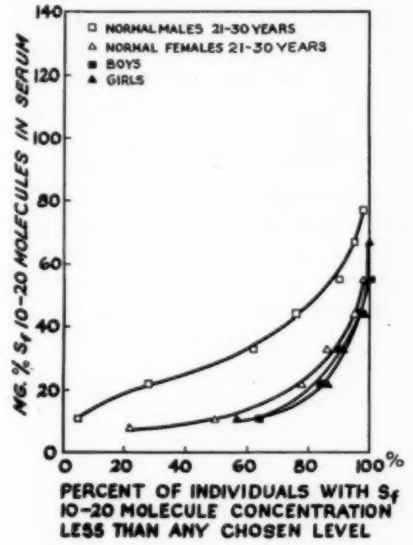

Fig. 5.—The level of S_f 10-20 molecules in the serum of children and of adults between 21 and 30 years of age.

birth to 15 years.* The results are plotted in Figs. 3 and 4.

It was found that male children all had S_f 10-20 levels below 55 mg. per cent, with 64 per cent of the children being below 11 mg. per cent, 85 per cent below 22 mg. per cent, 90 per cent below 33 mg. per cent, and 96 per cent below 44 mg. per cent. The values obtained in these boys were significantly lower than those previously determined for normal male adults.[3]

Female children all had S_f 10-20 levels below 66 mg. per cent, with 57 per cent being below 11 mg. per cent, 85 per cent below 22 mg. per cent, 90 per cent below 33 mg. per cent, and 97 per cent below 44 mg. per cent. The levels for normal female children approximate the range for the young normal female adults, as shown in Fig. 4.[3]

*The values here reported for the S_f 10-20 range exclude the S_f 10 fraction itself.

Fig. 5 shows the similarity of values for normal male and female children, as well as their proximity to those obtained for normal female adults ranging in age from 21 to 30 years. Normal male adults of the same age group show significantly higher titers throughout.

High levels of S_f 10-20 molecules frequently have been found in the sera of women during, and immediately after, pregnancy.[3] In twelve women and their infants studied shortly after birth, there was no correlation between the concentrations present in the sera of the mothers and newborn infants, and in every instance the levels were lower in the infants' sera than in that of their mothers (Fig. 6).

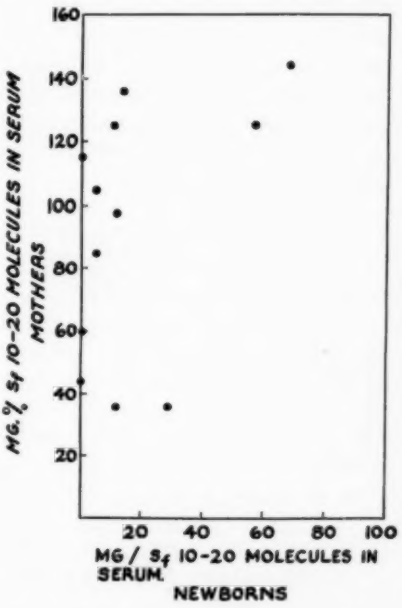

Fig. 6.—Relation of the levels of S_f 10-20 molecules in newborn infants and their mothers. There was no correlation between these levels although in every instance the concentration is lower in the infant's serum than in that of the mother.

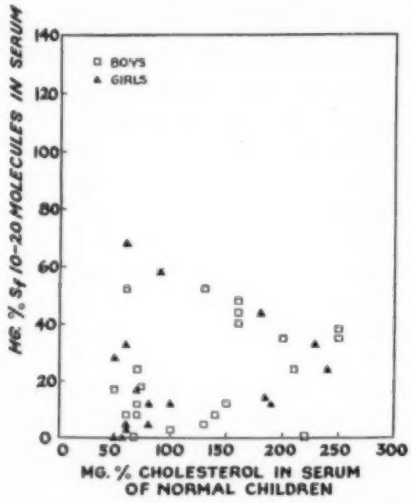

Fig. 7.—Relation of the serum cholesterol to the concentration of S_f 10-20 molecules in the serum of children. There is no appreciable correlation between these two blood constituents in normal children.

In Fig. 7 the levels of S_f 10-20 molecules are plotted against the analytical serum cholesterol levels of thirty-five normal children. In this study there was no significant correlation between the total serum cholesterol and the level of the S_f 10-20 class.

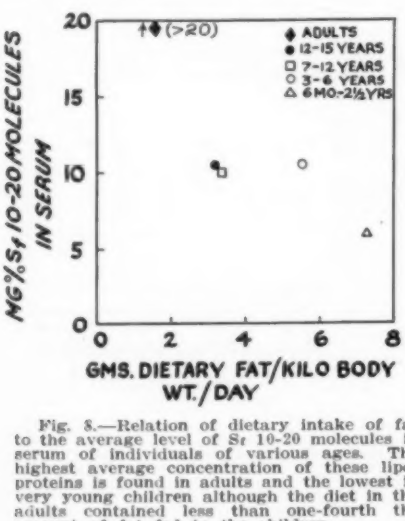

Fig. 8.—Relation of dietary intake of fat to the average level of S_f 10-20 molecules in serum of individuals of various ages. The highest average concentration of these lipoproteins is found in adults and the lowest in very young children although the diet in the adults contained less than one-fourth the amount of fat fed to the children.

In an attempt to determine whether the level of S_f 10-20 molecules in the pediatric age group is related to the daily intake of dietary lipids, a correlation was sought between the number of grams of dietary fat per kilogram of weight per day, and the level of S_f 10-20 molecules in the serum at five age ranges. The highest average values of S_f 10-20 molecules is found in adults whose average daily fat intake per kilogram of body weight is 1.6 grams (Fig. 8). On the other hand, children from 6 months to 2½ years, whose average daily intake of fat per kilogram of body weight is more than four times as high (approximately 7.3 grams of fat per kilogram), show significantly lower average levels of S_f 10-20 molecules (average—6 mg. per cent). This would indicate that children can tolerate a much higher intake of fat per unit of body weight than adults without showing comparable increases in concentration of the S_f 10-20 molecules.

DISCUSSION

The study of atherosclerosis in the human being has of necessity been an indirect one, since direct examination of tissues in the living subject is seldom possible, and the establishment of experimental studies with adequate controls is well nigh impossible. Using rabbits as the experimental animal, all recent reports have confirmed earlier observations by Ainitschkow,[5] who demonstrated that cholesterol feeding in the rabbit can result in the production of hypercholesterolemia and of lesions in the arteries greatly resembling those found in human arteriosclerosis. Gofman and associates[1] showed that a lipoprotein of the S_f 5-10 class of molecule is present in variable concentration in the serum of

all normal rabbits. During cholesterol feeding, these molecules increased in concentration first, and following the rise in concentration of the S_f 5-10 class of molecules most rabbits, as a result of further cholesterol feeding, began to develop increasing concentration of molecules of the S_f 10-30 class. Autopsy of the rabbits at the end of a fifteen-week feeding period, showed that the degree of atherosclerosis was greater, the higher the final concentration of molecules of the S_f 10-30 class, while animals with minimal concentration of such molecules had little or no gross atheroselerosis. In contrast with the molecules of the S_f 10-30 class, the concentration of lipoproteins in the S_f 5-10 class did not show any correlation with the extent of development of atherosclerosis.

This evidence would indicate that exogenous cholesterol can, in the rabbit, be a factor in the etiology of atherosclerosis. The appearance of "abnormal" molecular fraction by increase in exogenous cholesterol then suggested the study of these fractions in a number of adult human subjects.

It was subsequently shown that while the "normal" adult had variable levels of macromolecules of S_f 10-20 group, patients with myocardial infarction, angina pectoris, diabetes, and nephrosis showed consistently higher levels of these molecules. In no case was it possible to demonstrate any acute effect on the blood concentration of S_f 10-20 molecules from a single meal. Testing numerous individuals on two or more occasions revealed that the level of S_f 10-20 molecules was essentially stable, provided that the subjects did not change their dietary habits. In adults, marked and prolonged reduction of fat intake usually did result in significant decrease of elevated S_f 10-20 levels. Our data show that infants ingesting more than four times the adult amounts of dietary fat per unit of body weight per day fail to show comparable levels of S_f 10-20 lipoproteins. This tends to indicate an endogenous factor in children which uniformly allows a greater tolerance of exogenous fat.

Previous reports[3] have indicated that while it is generally true that the S_f 10-20 level is elevated with a rise in blood cholesterol, the deviations from this rule are frequent and marked so that the total blood cholesterol level is of little value in predicting the S_f 10-20 level in a particular patient. A similar lack of correlation was found in the present study with some of the highest concentrations of these lipoproteins being found in children whose total serum cholesterol levels were under 100 mg. per cent.

Although a significant difference has been found in the levels of S_f 10-20 lipoproteins between the sexes in the 21 to 30 age group, our studies show that between birth and 15 years of age the levels of lipoproteins are the same for the two sexes. In children, the levels approximate those found in women 21 to 30 years old, but are lower than those found in older women, and are significantly lower than those reported in adult males of any age group.

The lipoprotein levels present in cord blood (in fifty-one newborn infants) were of the same magnitude as those found in the total group of children. In all cases the cord blood had lower concentrations than that of the infant's mother taken at the same

time, but there was no correlation between the blood level of the infant and mother.

SUMMARY

Determinations of the concentration of certain lipoprotein molecules (S_f 10-20 class) are reported for 147 normal children ranging in age from birth to 15 years. These molecules previously have been shown to be associated with atherosclerosis.

Similarity of values was found for normal male and female children.

Boys had significantly lower values than those previously determined for normal male adults, but the levels for girls approximate the range for young normal female adults.

No correlation was present between the concentrations of these lipoproteins in the sera of newborn infants and their mothers.

No significant correlation was noted between the total serum cholesterol and the level of the S_f 10-20 class.

The data presented would indicate that children can tolerate a much higher intake of fat per unit of body weight than adults without showing comparable increases in concentration of the S_f 10-20 molecules.

Appreciation is expressed to Sheldon Cook, M.D., and Richard L. Anderson, M.D., for obtaining some of the blood specimens studied.

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THE LIPOPROTEINS OF SERUM IN INFANCY AND CHILDHOOD

II. Lipoprotein Levels in Juvenile Diabetes Mellitus

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San Francisco, Calif.

IT IS well known that persons with diabetes mellitus tend to develop atherosclerosis and associated illnesses at an earlier age than nondiabetic individuals. Gofman and associates have shown that people with atherosclerotic manifestations tend to have higher-than-normal blood levels of S_f 10-20 lipoproteins, as determined by analytical ultracentrifugation.[1-3] In the light of these findings it was felt that measurements of this fraction in the blood of juveniles with diabetes mellitus might reveal differences when compared with values obtained in "normal" children. Attempts could then be made to correlate such differences with any of the aspects of a particular child's diabetic state.

This paper deals with a series of forty-six juvenile diabetics on whom levels of S_f 10-20 lipoprotein molecules were determined. These levels were compared with previously reported normals[4] and an attempt made to correlate them with such variables of diabetes mellitus as the sex of the patient, duration of the disease, degree of control, severity of the condition ("per cent diabetic"*), dietary intake of fat per unit of body weight, the weight of the individual, and serum cholesterol.

There were twenty-six males and twenty females from the Pediatric Diabetic Clinic of the University of California Hospital. Complete information regarding the past history, physical status, course of the disease, diet, insulin dosage, and degree of control was available for all patients. The methods of analysis have been reported previously.[4]

RESULTS

The results of measurements of the concentration of S_f 10-20 lipoprotein molecules† on forty-six juvenile diabetics, ranging in age from 7 to 20 years, are plotted in Fig. 1, along with those previously reported for normal children.[4]

It was found that all the male juvenile diabetics had levels below 66 mg. per cent, with 38 per cent being below 11 mg. per cent, 62.0 per cent below 22 mg. per cent, 81 per cent below 33 mg. per cent, 92 per cent below 44 mg. per cent, and 96 per cent below 55 mg. per cent. The highest concen-

From the Division of Pediatrics, University of California School of Medicine, San Francisco, and the Donner Laboratory, Division of Medical Physics, and the Radiation Laboratory, Berkeley.

This work in part was supported by the United States Public Health Service.

*"Per cent diabetic" $= \dfrac{\text{Total daily insulin dose in units} \times 100}{(\text{Grams of carbohydrate}) + (\text{Grams of protein} \times 0.58) + (\text{Grams of fat} \times 0.1) \times \frac{1}{2}}$

†The values here reported for S_f 10-20 range exclude the S_f 10 fraction itself.

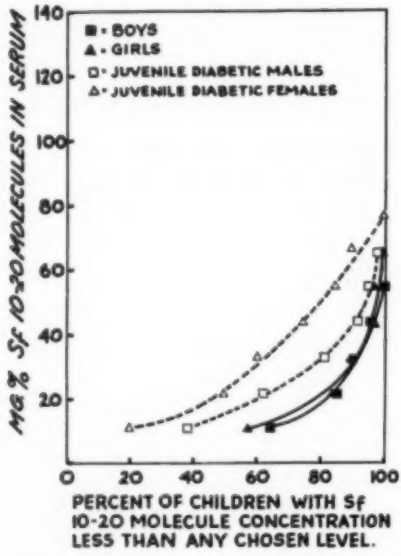

Fig. 1.—The level of Sf 10-20 molecules in the serum of normal children (solid lines) and children with diabetes mellitus (dotted line). The values obtained for the normal children were significantly lower than those for the diabetics.

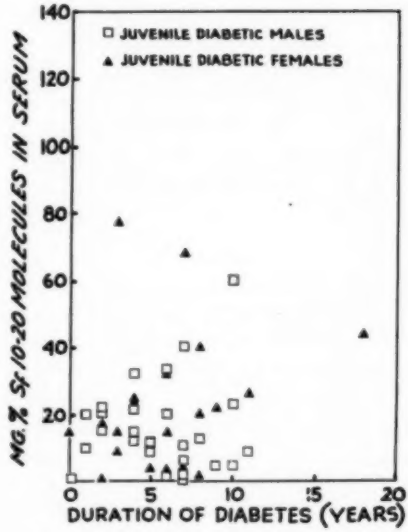

Fig. 2.—Relation of the level of Sf 10-20 lipoprotein molecules in the sera and the duration of the diabetic state. No close correlation was found.

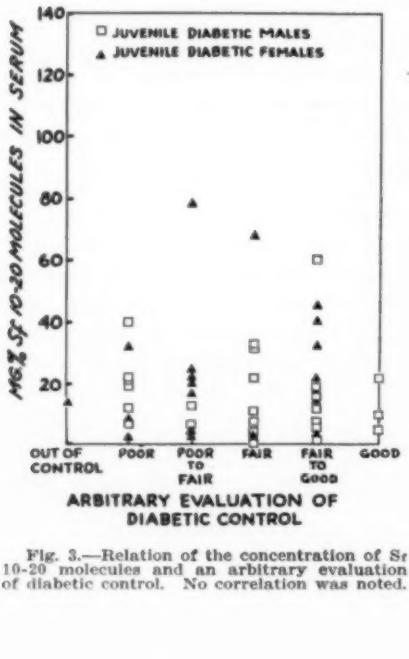

Fig. 3.—Relation of the concentration of Sf 10-20 molecules and an arbitrary evaluation of diabetic control. No correlation was noted.

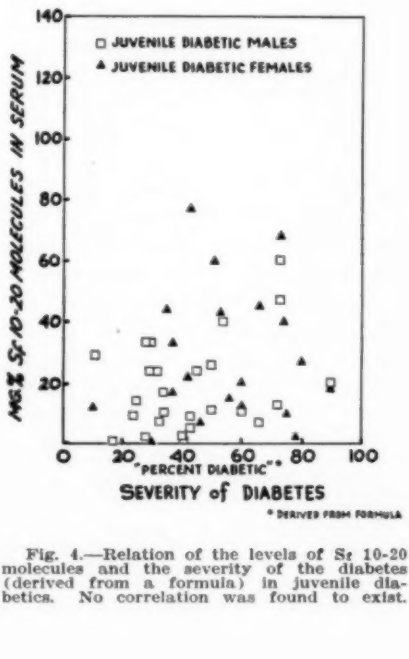

Fig. 4.—Relation of the levels of Sf 10-20 molecules and the severity of the diabetes (derived from a formula) in juvenile diabetics. No correlation was found to exist.

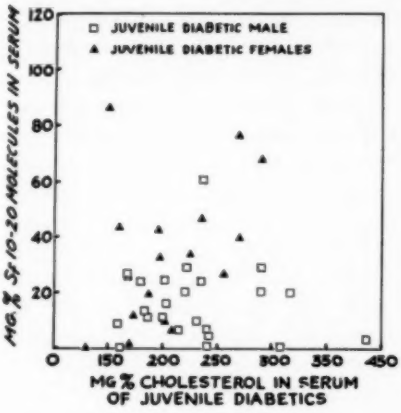

Fig. 5.—Relation of the serum cholesterol to the concentration of S_f 10-20 molecules in the serum of juveniles with diabetes mellitus. No marked correlation is apparent.

tration of serum lipoproteins in a diabetic girl was 76 mg. per cent, with 20 per cent being below 11 mg. per cent, 50 per cent below 22 mg. per cent, 60 per cent below 33 mg. per cent, 75 per cent below 44 mg. per cent, 85 per cent below 55 mg. per cent, and 90 per cent below 66 mg. per cent.

The values for diabetic girls were higher than those for diabetic boys. The values for diabetic boys were higher than those previously reported for normal male children. Diabetic girls, too, tend to have higher levels of lipoproteins than their normal counterparts.

No close correlation was found in this age group between the level of S_f 10-20 lipoprotein molecules in the sera and the duration of the diabetic state (Fig. 2). An attempt was made to establish an arbitrary evaluation of the degree of control of each patient. This was a subjective conclusion based on the history and results of the physical examination as well as periodic determination of serial blood sugar levels, excretion of sugar in urine over twenty-four-hour periods, and the course of the disease during the previous months. The control of each patient was graded on a scale from "poor" to "good." No correlation was found in this age group between the lipoprotein concentration and the degree of control (Fig. 3).

There was no direct correlation between lipoprotein levels and the severity of the disease, as determined by calculated percentage of the exogenous insulin requirement that was necessary to maintain the patient in good control (Fig. 4). However, using the formula for "per cent diabetic," it was found that the male in this study tended to have a milder disease than the female, with the average boy being

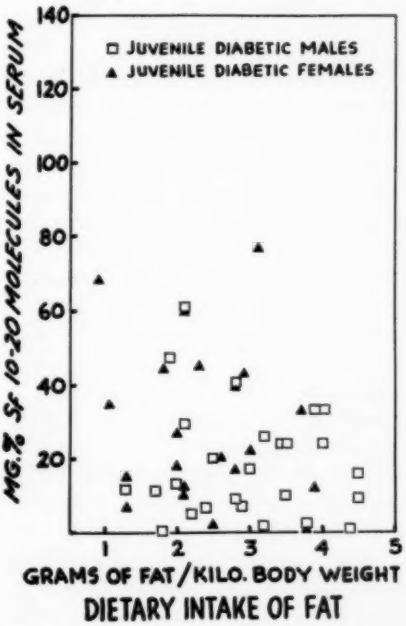

Fig. 6.—Relation of the dietary intake of fat per kilogram of body weight and the levels of S_f 10-20 lipoprotein molecules in diabetic children. The average intake of fat is higher in the boys than in the girls, although male diabetes have lower lipoprotein levels than females.

"43 per cent diabetic," while the average girl was "55 per cent diabetic." This difference may be accounted for by the increased physical activity of boys in this age group, which would tend to lower insulin requirement.

In Fig. 5 is shown the relationship between the analytic serum cholesterol levels and the concentrations of S_f 10-20 lipoprotein molecules. No marked correlation is apparent.

The dietary intake of fat per kilogram of body weight had no demonstrable effect on the level of S_f 10-20 lipoprotein molecules in these children (Fig. 6). Although male diabetics have lower lipoprotein levels than females, their average intake of fat is higher (3.0 grams per kilogram) than the girls (2.5 grams per kilogram).

DISCUSSION

The frequent complication of infection and premature aging still encountered in the face of continued insulin therapy of the young diabetic patient and the still-shortened life expectancy of these patients represents a distinct challenge to the medical profession. Quite often the patient has borne the blame for these complications, or their occurrence has been regarded as inevitable.

There is no uniformity of opinion regarding the importance of dietary restriction and control in the development of the complications of diabetes, especially atherosclerosis, hypertension, nephropathy, arcus senilis, etc. It would appear that insulin replacement alone cannot prevent these complications. We are now able to maintain apparently adequate control of the diabetic patient as regards blood sugar, urinary excretion of reducing substance, growth, sexual development and maturation. We are increasingly able to control bacterial infection. However, we are still unable to control these threats to a normal life span in many cooperative patients, under apparently adequate diabetic control.

A correlation has been shown to exist between elevated levels of lipoprotein of the S_f 10-20 class and idiopathic atherosclerosis.[1-3] A prolonged restriction of the dietary intake of fats has resulted in a marked reduction in the elevated blood levels of S_f 10-20 lipoproteins. Further work may show that this is a method of combating the development of atherosclerosis. The idea suggests itself that a reduction of the lipoprotein fraction of the blood by suitable dietary restriction of fat might also result in a decreased incidence of atherosclerosis in the diabetic patient. This method of attack is now under study.

In a previous report on seventy-six adult patients with diabetes mellitus, between the ages of 20 and 80 years, it was demonstrated that females have distinctly higher incidence of S_f 10-20 lipoprotein molecules than do normal females in all age categories.[2] The effect is relatively great in the diabetic females between the ages of 20 and 40 years. It was also found that the same general effect was observed in diabetic males as compared to normal males, but is not as large as for the females. Our studies also showed that the juvenile diabetic female has greater levels of S_f 10-20 lipoprotein molecules than the male, and that both have higher blood levels of the S_f 10-20 class than their normal counterparts.

SUMMARY

Determinations of the concentration of certain lipoprotein molecules (S_f 10-

20 class) are reported for forty-six juveniles with diabetes mellitus.

Diabetic girls and diabetic boys have higher levels than their normal counterparts. The values for the girls were higher than those for boys.

No close correlation was found in this age group between the level of S_f 10-20 lipoprotein molecules in the sera and (1) the duration of the diabetic state, (2) the degree of control, (3) the severity of the disease, (4) the analytic serum cholesterol levels, or (5) the dietary intake of fat per unit of body weight.

Appreciation is expressed to Thomas L. Nelson, M.D., and John P. Conrad, M.D., for obtaining some of the blood specimens studied.

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APLASTIC ANEMIA IN SIBLINGS WITH MULTIPLE CONGENITAL ANOMALIES (THE FANCONI TYPE)

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PRIMARY, idiopathic aplastic anemia is an acute or chronic disease which is progressive and ultimately fatal. The etiology is unknown. In a child who has previously been well the onset is usually insidious. The hemogram is characterized by a marked reduction in the number of erythrocytes, which are hyperchromic and macrocytic. The white blood corpuscles are also markedly reduced and disclose a decrease in the neutrophiles with a relative increase in the lymphocytes. The platelet count is markedly reduced. The reticulocyte count is usually markedly lowered, although reticulocytosis has been demonstrated in several cases reported in the literature. There is no evidence of regeneration or destruction. Immature cells are rarely seen. The bone marrow reveals various degrees of degeneration or complete atrophy.

Estren and Dameshek[1] described eight cases of familial hypoplastic anemia of childhood occurring in two families. No other congenital anomalies were found in these cases. They, therefore, concluded that the etiological factor in the production of aplastic anemia could be traced to a defect in the chromosomal mechanism associated with the development of the bone marrow.

In 1927, Fanconi[2] described three brothers with hypoplastic anemia. The children were 5, 6, and 7 years of age. The hemograms disclosed hyperchromic anemia, leucopenia, and thrombopenia. Other associated abnormalities were microcephaly, convergent strabismus, hypoplasia of the testicles, hyperactive deep tendon reflexes, brownish melanin-like pigmentation of the skin without involvement of the buccal mucosa. He noted marked hemorrhages in all of these cases. The bone marrow was hypoplastic and, in Fanconi's opinion, was another manifestation of a constitutional defect.

Émile-Weil,[3] Hjorth,[4] and Dacie and Gilpin[5] reported familial cases of hypoplastic anemia with associated congenital abnormalities, the so-called "Fanconi type" of anemia. Uehlinger,[6] van Leeuwen,[7] Émile-Weil,[3] Estren, Suess, and Dameshek,[8] and Beautyman[9] reported single instances of this syndrome. Diamond[10] mentions that three cases have come to his attention in the last twenty years.

Two siblings, one when he reached the age of 6 years, the other when he was 6½ years, presented the clinical picture of aplastic anemia associated with several congenital anomalies. These cases were similar to those reported in the literature as examples of the "Fanconi type" of aplastic anemia.

CASE REPORTS

CASE 1.—A. W. (No. 20514), a white, male child, 6½ years of age,

From the Department of Pediatrics of the Jewish Memorial Hospital, New York City, New York.

was admitted to the Jewish Memorial Hospital on June 23, 1941. He had been in excellent physical condition up until October, 1940. Following a tonsillectomy at this time, the mother noticed pallor and asthenia. The family physician, Dr. M. Jaffin, who had observed the child from birth, was consulted. He found that the child had a moderate anemia, and gave him iron orally, and liver by subcutaneous injections. A diet adequate in vitamins was prescribed. No improvement was noted following this therapy. The asthenia and anemia became more pronounced. Poor appetite and frequent vomiting were noted.

The family history was not remarkable, except for a consanguineous marriage on the maternal side. The grandparents were first cousins. There was no history of any abnormalities in either the maternal or the paternal families. Another sibling, 1½ years of age, was absolutely normal at this time.

Physical examination on admission to the hospital revealed a child with extreme pallor and a melanin-like appearance of the skin. Multiple congenital anomalies were obvious. Plastic surgery for correction of atresia of both ear canals had been performed at the age of 2 years. The child had a diminution of hearing and employed lip reading. Bone conduction was normal. Air conduction was reduced by 50 decibles on one ear and 60 on the other. There was ptosis of both eyelids. Fundus examination revealed a whitish appearance of both nerve heads with a vertical eliptical con-

Fig. 1. (Case 1).—Photograph of A. W., showing "café au lait" spots, vitiligo, deformity of ear auricles, ptosis of eyelids, microphthalmia, and abnormalities of thumbs.

figuration, suggesting either a pseudoneuritis or papilledema. The visual fields were normal and the opthalmologist concluded that the condition was a pseudoneuritis probably due to a refractive error, rather than a papilledema, inasmuch as the appearance of the eye grounds remained the same over a period of months. Examination for color blindness revealed normal perception for color. The sense of smell was tested and found to be normal. In addition to the brownish tint of the skin of the body, vitiligo on the back of the right shoulder and "café au lait" spots in the right axillary line were noted. A layer of freckles was seen in the left scapular region. No tumors were palpable in the skin and subcutaneous tissues. The dermatologist considered this an aborted type of von Recklinghausen's disease, since this condition is usually associated with other congenital abnormalities. An overgrowth of hair (hirsutism) on the arms and chest was prominent. A loud systolic murmur could be heard over the entire precordium, but this had not been present previous to the onset of the anemia and was obviously hemic. The liver and spleen were palpable. The right thumb was attached to the hand by a fold of skin. The thumb on the left hand had restriction of movement and was thinner than is usually seen, resembling a finger rather than a thumb. It should be noted that the child was of a superior intelligence. (Fig. 1.)

The hemogram on June 23 was hemoglobin 23 per cent (Sahli); red blood cells, 1,300,000 per cubic millimeter; white blood cells, 2,450 per cubic millimeter; segmented neutrophiles, 24 per cent; nonsegmented neutrophiles, 7 per cent; eosinophiles, 3 per cent; lymphocytes, 55 per cent; monocytes, 10 per cent. The blood counts consistently showed a low hemoglobin, varying between 18 and 44 per cent with the red blood cell count from 920,000 per cubic millimeter up to 2,800,000 per cubic millimeter. The white blood cell count was reduced from 3,200 to 1,900 per cubic millimeter. The lymphocytes were as high as 75 per cent of the differential count. The monocytes also were as high as 18 per cent. Anisocytosis, hyperchromia, and polychromasia were seen consistently. There were also macrocytic hyperchromic red cells. The hematocrit reading was 11 mm. The reticulocytes were only 0.8 per cent. Three transfusions of 200 c.c. each were given on June 28, July 5, and July 15. The blood Wassermanns of the patient and his parents were negative. Hemograms of the parents and the other sibling were normal. Roentgenograms of the skull, long bones, and heart and lungs were normal. X-ray examination of the wrists showed an absence of the metacarpal bone of the right thumb and a rudimentary proximal phalanx. The carpal centers were reduced in number on both wrists. Electrocardiograms showed a normal sinus rhythm and no abnormality. The blood chemistry disclosed: sugar, 85 mg. per cent; urea nitrogen, 17.5 mg. per cent; cholesterol, 165 mg. per cent; cholesterol esters, 83.2 mg. per cent; calcium, 10.4 mg. per cent; phosphorus, 4.1 mg. per cent; and phosphatase, 4.3 Bodansky units. The icteric index was 5.1. The van den Bergh direct reaction was negative; the indirect reaction showed a trace. The bleeding and coagulation times were normal. The blood platelets were reduced to 90,000 per cubic millimeter. There was poor clot retraction at the end of twenty-four hours. Increased resistance of the red blood corpuscles was noted. Hemolysis began at 0.4 per cent saline solution and was not completed at 0.3 per cent. The gastric analysis disclosed a diminution of the free and combined hydrochloric acids. The urine was negative. A sternal marrow puncture was performed and disclosed the following:

Total nucleated cell count	15,500
Myeloblast	4%
Premyelocyte	3%
Myelocyte	4%

Metamyelocyte	3%	
Band form neutrophile	6%	
Mature polymorphonuclear neutrophile	18%	
Mature eosinophile	1%	
Lymphocyte	20%	
Plasma	1%	
Monocyte	1%	
Erythroblast	9%	39%
Normoblast	30%	

There was a marked hypocellularity of the erythroid, myeloid, and megakaryocytic bone marrow cells supporting the diagnosis of aplastic anemia. There was a disturbance of the erythroid-myeloid ratio with nearly three times the usual number of young red forms.

Ferrous sulfate 3 grains and dilute hydrochloric acid 5 minims were administered orally three times a day. Vitamin B complex 1 c.c. (Lilly) and 1 c.c. of a solution of crude liver extract, 2 U.S.P. units per cubic centimeter were given by injection daily without any effect upon the hemogram. The child was discharged on July 17 and sent to a resort for convalescent care, where all of the above-mentioned therapy was continued.

On September 24, the patient was readmitted to the hospital and examination disclosed a hemoglobin of 22 per cent; red blood cells, 1,220,000 per cubic millimeter; white blood cells, 1,550 per cubic millimeter; segmented neutrophiles, 23 per cent; nonsegmented neutrophiles, 4 per cent; eosinophiles, 3 per cent; lymphocytes, 63 per cent; monocytes, 3 per cent; normoblasts, 5 per cent; with anisocytosis. The reticulocytes were only 0.15 per cent. The red blood cells showed increased resistance. Hemolysis began at 0.4 per cent saline solution and was not complete at 0.3 per cent. The coagulation time was 7 minutes (capillary tube method), the bleeding time 3 minutes, and the platelet count 120,000 per cubic millimeter. Dessicated thyroid extract 1 grain daily had been started one week previous to this admission and was continued. It was thought advisable to extend this therapy for a few weeks to see whether there would be any stimulation of the bone marrow, since hypothyroidism may be responsible for hypoplastic anemias simulating primary aplastic anemia.[11] Transfusion was withheld and the child was discharged on September 27, with instructions to continue iron, liver, hydrochloric acid, thyroid extract, and high vitamin diet.

The boy was admitted for the third time on October 14. Despite the fact that he had received 2 grains of dessicated thyroid extract daily for several weeks, together with all of the other therapy, there was no response as shown in his blood picture. The hemoglobin had fallen to 18 per cent and the red blood cells to 960,000 per cubic millimeter. Large macrocytes, marked hyperchromia of the red blood cells, and practically no platelets were seen. The child was alert and able to play with the other patients in spite of his profound anemia. Neurological examination disclosed no involvement of the pyramidal tracts or of the posterior cord columns. The basal metabolic rate was minus 6. There was a reversal of the relative measurements of the upper and lower trunk, the lower being about one and one-half times longer than the upper. The measurements of the child were: crown to heel, 108 cm.; crown to pubis, 53.5 cm.; pubis to heel, 54.5 cm.; outstretched arms, 108.5 cm. between the tips of the middle fingers; circumference of the skull, 48.25 cm. Blood serum sodium chloride was 109 meq. per liter and serum sodium 147.1 meq. per liter. X-ray examination of both wrists revealed one additional center of under-developed ossification in the right wrist.

A blood culture was sterile. Transfusions were given on October 15, 200 c.c.; October 20, 250 c.c.; and October 28, 200 c.c. He was discharged on November 1. His response to transfusions had not been satisfactory. The parents were advised to return to the hospital at stated periods for supportive transfusions. Ophthalmo-

scopic examinations during these three hospital admissions disclosed the same picture as described originally. This fact is noteworthy in view of subsequent findings.

The child was readmitted for the fourth time on November 18, with a profound anemia. His hemoglobin had fallen to 15 per cent; red blood cells to 890,000 per cubic millimeter; white blood cells to 1,350 per cubic millimeter. The lymphocytes were 70 per cent; segmented neutrophiles, 16 per cent; nonsegmented neutrophiles, 10 per cent; and monocytes, 4 per cent. The reticulocyte count was only 0.3 per cent. The hematocrit reading was 11 mm., which is 25 per cent of normal. The platelet count varied between 55,000 and 30,000 per cubic millimeter. The red blood cells still showed increased resistance. There was no clot retraction after thirty-two hours. The spleen was palpable. He had recurring epistaxis. Many purpuric spots on the legs and arms and large areas of ecchymosis were seen over the trunk and extremities. With all of these symptoms and profound anemia the child was energetic enough to get out of bed and play with the other children. A sternal marrow biopsy was performed on November 29 and disclosed a grossly fatty marrow. Following this procedure there was considerable bleeding from the site of operation and the child presented a picture of shock. Local pressure, thromboplastin, and transfusion controlled the bleeding. The child became progressively worse and had hematemesis and melena. On December 9 he complained of headache and was drowsy. This was followed by vomiting and amaurosis. At this time he was delirious and comatose. A diagnosis of intracranial hemorrhage was made. Eye ground examination disclosed large hemorrhages in both eyes in the macular region with beginning macular holes and several areas of vitreous hemorrhage. The platelet count now was only 21,000 per cubic millimeter; coagulation time four minutes; bleeding time prolonged beyond ten minutes; and there was no clot retraction after seventy-two hours. Transfusions were given on November 19, 250 c.c.; November 23, 250 c.c.; November 29, 350 c.c., December 5, 450 c.c.; and December 9, 450 c.c. The child expired on December 13.

Necropsy Report.—The autopsy was performed by Dr. Alfred Schwarz on Dec. 13, 1941. The positive pertinent data are included.

The skin is rather pale and the body is quite emaciated. There are several vitiliginous and hyperpigmented spots throughout the body surface. The right hand shows an anomaly inasmuch as the metacarpal bone of the thumb is missing, leaving a rudimentary thumb attached to the hand only by a thin skin bridge.

On opening the cranial cavity, diffuse and patchy quite recent subdural hemorrhages are found. The subarachnoidal space also contains patchy areas of hemorrhage at the convexity, the base, and the cerebellar surface of the brain. The brain is rather soft and friable in consistency, the right lobe being somewhat larger than the left, and the convolutions somewhat flattened. On section there is a massive hemorrhage on the medial aspect of the right occipital lobe measuring about 4 cm. in diameter. Another smaller rounded hemorrhage is found in the subcortical region of the left frontal lobe measuring about 1½ cm. The ventricles are somewhat dilated. Section of frontal lobe shows massive hemorrhage extending to subarachnoid space. The vessels are markedly dilated. Brain tissue shows some vacuolization and prominent pericellular spaces.

The left eye is removed for examination. On section through this globe the retina is found to be detached in its entire circumference, and a massive subretinal hemorrhage which extends well into the vitreous body is seen. Sections of the globe (Fig. 2) show

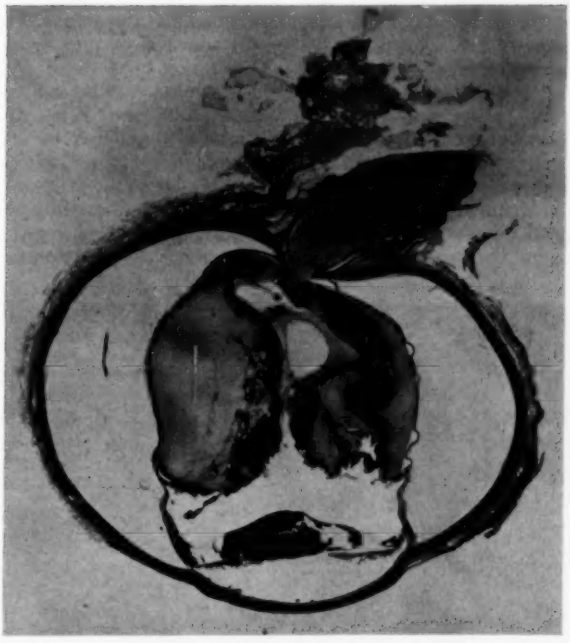

Fig. 2. (Case 1).—Photomicrograph (enlarged 4½ times) of a celloidin section of the globe, showing retinal detachment, edema of disc, and intact anterior segment.

Fig. 3 (Case 1).—Photomicrograph (enlarged 33 times) of a section of the optic nerve and papilla, showing edema of disc with forward bowing of cribiform fascia and lateral displacement of retinal margins. Note retinal detachment.

intact chambers, cornea, lens, sclera, and ciliary body, and confirm the detachment of the retina, with massive underlying hemorrhage, with some albuminous fluid beneath and blood in the retina. The retina shows prominent vacuolization and distortion of its layers and one area of glial proliferation and another area of complete disorganization of structure. The papilla shows edema and hemorrhage with elevation and some forward bowing of the cribiform fascia and lateral displacement of retinal margin at the borders of the papilla (Fig. 3). In this region there is considerable subretinal edema and hemorrhage.

The ribs are sectioned and found to be rather pale. There are several patchy hemorrhages throughout the bone marrow, which has a definite brownish tinge. The vertebral bodies show a rather pale slightly brownish bone marrow. Microscopic study of vertebral marrow reveals outstanding and marked hyperplasia with only a scattering of foci of hemopoesis and myelopoesis. The marrow fat shows some embryonal cells, and some myxomatous areas can be seen. Erythrophagocytosis and pigmentation are noted. In some areas of the marrow, intravascular erythropoesis is distinctly more prominent with only a scattering of extravascular myeloid cells. Areas of hemorrhage and adjacent fibrosis are seen. Some sections of bone marrow show marked and outstanding atrophy of tissue with the fat tissue of the marrow showing only a minimal sprinkling of intravascular erythropoesis (Fig. 4).

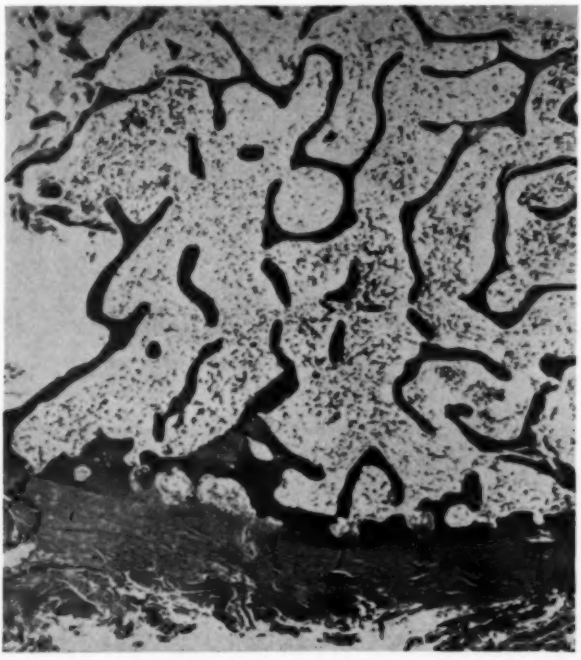

Fig. 4. (Case 1).—Photomicrograph (enlarged 11 times) of a section of the bone marrow, showing osteoporosis and fatty replacement with only an occasional focus of hematopoiesis.

The adrenal is atrophic with the zone of glomerulosa rather thin and showing vacuolization of the cytoplasm. The medulla is not included

in the section. Another section shows characteristic medullary tissue with rather prominent chromaffin content. The glomerulosa zone throughout all sections shows a prominence of rather fibrillar tissue and retraction of the epithelium.

The lymph node shows blood content with sinusoids suggesting hemorrhagic lymph node. The lymphoid tissue is unremarkable with only an occasional follicle. Another lymph node shows erythrophagocytosis with lymphatic stasis in the sinusoids. The pigmentation and erythrophagocytosis in some nodes are very prominent.

The spleen shows congestion of pulp proper, some definite myeloid elements in the pulp, evident erythrophagocytosis by reticulum cells, some active follicles with rather prominent Fleming corpuscles. No true erythropoesis in the isolated islands is evident.

Anatomical Diagnoses.—Aplastic anemia; extensive hemorrhages of right occipital lobe, massive left frontal lobe, massive subarachnoidal space, diffuse subdural space, diffuse subdural space of optic nerve, massive retinal hemorrhage, detachment of retina with hemorrhage into vitreous and subretinal space, extensive stomach hemorrhage and massive mucosa and lumen hemorrhage of gastrointestinal tract; ecchymotic and petechial hemorrhages of bone marrow, larynx, epicardium, lungs, endocardium, and myocardium; erythrophagocytosis of lymph nodes and spleen; hemosiderosis of liver, spleen, and bone marrow; congenital absence of right kidney; hypertrophy of left kidney with double ureter; hypoplasia of right adrenal; congenital absence of right first metacarpal bone; vitiligo, and congenital deformity of ears.

Cause of death: Massive hemorrhage into gastrointestinal tract in a case of aplastic anemia with multiple congenital anomalies.

TABLE I. HEMATOLOGY (CASE 1)

1941	HB. (%)	R.B.C.	W.B.C.	SEGMENTED NEUTROPHILES	NONSEGMENTED NEUTROPHILES	EOSINOPHILES	BASOPHILES	LYMPHOCYTES	MONOCYTES	RETICULOCYTES, PLASMODIA MYELOID CELLS. ETC.
6/23	23	1.330	2,450	24	7	3		55	10	Turk cells 1, anisocytosis poikilocytosis, polychromasia
7/ 5	32	2.800	3,200	53	3			28	18	Macrocytic hyperchromic R.B.C.
7/17	48	2.600	2,500	28	4		2	65		Plasma cell 1
9/10	20	1.200	2,250	22	2			75	3	Poikilocytosis, anisocytosis, achromia, large macrocytes, hypochromia
					Third Admission					
10/14	16	0.680	1,950	27	6	3		60	4	Anisocytosis, poikilocytosis macrocytes
10/31	28	1.580	3,200	10	5	2		75	8	
					Fourth Admission					
11/18	15	0.890	1,350	16	10			70	4	Anisocytosis, poikilocytosis macrocytes
11/27	22	1.190	1,300	12	12	2		70	4	Reticulocytes 1.45%
12/ 3	16	0.870	1,850	34	12	1		49	4	Reticulocytes 0.4%
12/11	22	1.870	2,100	35	17			34	14	Central achromia

TABLE II. HEMATOLOGY (CASE 1)

DATE	COAGULATION (MIN.)	BLEEDING (MIN.)	CLOT RETR. (MIN. TO HR.)	PLATELETS	R.B.C. FRAGILITY		SEDIMENTATION RATE (MM. IN MIN.)	HEMATOCRIT (MM.)	BLOOD CULTURE	WASSERMANN
					INITIAL HEMOLYSIS	COMPLETE HEMOLYSIS				
6/23	4	4½		90,000						
6/25					0.45%	0.3%	75 mm. in 15 min.; 165 mm. in 1 hr.			
6/26			poor at end of 24 hr.							
7/ 1										Father (neg.) Mother (neg.) Patient (neg.)
7/ 2				90,000						
9/25	7	3		120,000	0.4%	not comp. at 0.3%				
10/17									negative	
10/31								9 (22.5% nor.)		
11/21				55,000	0.4%	not comp. at 0.3%		11 (28% nor.)		
11/27				30,000						
12/ 3				30,000						
12/ 4			none after 32 hr.							
12/12				21,000						
12/13	4	more than 10								
12/15			none after 72 hr.							

TABLE III. BLOOD CHEMISTRY AND LABORATORY FINDINGS (CASE 1)

	WHOLE BLOOD			SERUM								
DATE	SUGAR (MG. %)	UREA (MG. %)	NACL (MG. %)	CHOLESTEROL (MG. %)	ICTERUS INDEX	VAN DEN BERGH	CA (MG. %)	P (MG. %)	PHOSPHATASE (UNITS)	CO_2 CAPACITY (VOL. %)	BASAL METABOLIC RATE	URINE
6/23												negative
6/24					5.1	d. neg. ind. tr.						
6/26	85	17.5		165 Esters 83.2								
9/24	90	9.2					10.4	4.1	4.3			negative
10/17	80	9.1	638 Na 338									
10/23											minus 6	
12/ 1					10.5	d. neg. ind. tr.						
12/13	150	12.0								53.0		

CASE 2.—I. W. (Hosp. No. 49984), a white, male, 6-year-old child of Hebrew extraction, was admitted to Jewish Memorial Hospital on March 25, 1946. He was the second sibling of A. W., described in the first case report. The child had been under my observation from 1942, since the death of his brother, A. W., from aplastic anemia with multiple congenital anomalies. Pallor was noted two weeks prior to admission, and a blood count revealed a reduction in all of the elements of the hemogram, including erythrocytes, leucocytes, and platelets.

Fig. 5. (Case 2).—Photograph of I. W., showing vitiligo, microphthalmia, and strabismus.

On March 18, the hemoglobin was 50 per cent; red blood corpuscles, 2,380,000 per cubic millimeter; white blood corpuscles, 5,400 per cubic millimeter; with a differential count of segmented neutrophiles, 11 per cent; nonsegmented neutrophiles, 20 per cent; lymphocytes, 66 per cent; monocytes, 3 per cent. There was marked poikilocytosis, polychromasia, macrocytosis, and target cells seen on the smear. The reticulocyte count was 0.3 per cent. The platelet count was 63,000 per cubic millimeter.

It is of interest that previous hematological examinations in 1941 and subsequently were all normal. Measles, chicken pox, and occasional upper respiratory infections were the only illnesses recorded previous to the present episode.

Physical examination revealed pallor, a palpable liver and spleen, strabismus, melanin-like brownish pigmentation of the skin with freckling and areas of vitiligo, and microcephaly (48.5 cm.). There was a pigmented scar a few inches above the left external malleolus where a benign nevus had been excised. Both eyeballs were very small. The pupils reacted to light and accommodation. Funduscopic examination revealed pallor of the disc and retina due to the anemia. Neurological examination was completely normal. The blood pressure was 110/70. The physical examination was otherwise not remarkable. (Fig. 5.)

X-ray examination of the skeleton revealed a definite delay in the appearance of the carpal centers. There was a double nucleus in the tarsal scaphoid.

On March 20, 1946, a transfusion of 250 c.c. of whole blood was administered. Sternal marrow aspiration was performed on March 28, 1946, and revealed the following: total nucleated cell count, 29,650 per cubic millimeter; premyelocytes, 1.0 per cent; neutrophilic myelocytes, 9.5 per cent; metamyelocytes, 3.5 per cent; basophilic myelocytes, 0.5 per cent; bands, 18.5 per cent; polymorphonuclears, 8.5 per cent; lymphocytes, 35.5 per cent; monocytes, 2.5 per cent; megaloblasts, 7.0 per cent; erythroblasts, 4.0 per cent; normoblasts, 10.5 per cent. The myeloid-erythroid ratio was 1.9:1.0. The marrow showed a distinct hypoplasia, both quantitatively and qualitatively. There was a moderate shift to the right in the white cell series with a shift to the left in the cells of the erythroid series. Megakaryocytes were rare. On this specimen the diagnosis of early aplastic anemia was made. The blood was type O and Rh positive. The Wassermann was negative. Bleeding, coagulation time, fragility,

and sedimentation rate were all normal. The hematocrit was 21 mm. and the blood corpuscular volume, 8 cubic microns. Blood examinations of the parents were normal. They were both Rh positive and type A. Their Wassermanns were negative. Blood chemistry revealed urea nitrogen, 13 mg. per cent; nonprotein nitrogen, 37.5 mg. per cent; uric acid, 3.75 mg. per cent; cholesterol, 119 mg. per cent; cholesterol esters, 82 mg. per cent; Alkaline phosphatase, 12 mg. per cent; and serum sodium, 325 mg. per cent. The urine was normal. Stool examination was negative. The basal metabolic rate was plus 11. He was discharged from the hospital and his blood picture was repeatedly determined.

Dr. Carl H. Smith saw the child in consultation. Bone marrow and peripheral blood studies were done by him. A report of the peripheral blood is recorded on April 27 (see Table IV). He expressed the opinion that the history, clinical course, and present hematological status are consistent with a progressive aplastic anemia.

Transfusions were given on subsequent admissions, April 30, 200 c.c.; August 8, 240 c.c.; September 10, 200 c.c.; October 29, 350 c.c. Despite a profound anemia (see Table IV) the child was very active and complained only of slight fatigue on exertion. Ecchymotic spots over several parts of the body were noted in the following month.

Nov. 19, 1946, he was readmitted because of hematemesis the previous night. In addition to transfusions, the child had been receiving iron and liver without any favorable response in the blood picture. A transfusion of 250 c.c. was administered on November 19, and folic acid therapy was introduced. The skin was much darker than previously observed. Large, preretinal hemorrhages were noted as well as one in the macular region of the left eye. It was our impression that there was a definite edema of both discs. Transfusion of 300 c.c. was given on December 9, because the child had a hemoglobin of only 30 per cent and was bleeding from the gums. A systolic murmur was heard over the heart (hemic). Large subcutaneous hemorrhages were seen on the extremities. Transfusions were administered on December 23, 250 c.c., and December 26, 250 c.c.

The final admission of this child was on Dec. 31, 1946. He had severe hematemesis and bleeding from the gums for the past twenty-four hours. These symptoms persisted for several days. Re-examination of the fundus disclosed marked edema, thrombosis of the central retinal vein, and marked pallor. The child became stuporous and expired on Jan. 14, 1947.

Necropsy Report.—The autopsy was performed by Dr. Alfred Schwarz on Jan. 14, 1947, the pertinent findings being included below.

The skin generally is pasty and whitish-yellow in color. There is evidence of occasional petechial hemorrhages and large hematomas. The heart is somewhat enlarged, mainly due to dilatation of the chambers. Its external surface contains multiple petechiae both large and small. Sections of heart show some endocardial hemorrhage. The papillary muscle shows extensive hemorrhage and some necrosis. There are some fatty changes.

The liver is of natural size and consistency, but its color is pasty yellow. On section this yellow color is rather prominent with minute, patchy-like yellow areas described throughout the entire parenchyma. Numerous petechial hemorrhages are found in the mucosa of the entire gastrointestinal tract. The spleen is small, firm, and shows on section a light red color and some preserved follicles. The pulp glistens. The adrenals are firm and small with a well-developed cortex and rather scant medulla. The kidneys are very light. They are firm, but their capsules strip with ease and their surfaces are smooth. Sections of kidneys show dilated tubules, some of them containing albuminous casts. There is some parenchymatous degeneration.

TABLE IV. HEMATOLOGY (CASE 2)

DATE	HB. (%)	R.B.C.	W.B.C.	SEGMENTED NEUTROPHILES	NON-SEGMENTED NEUTROPHILES	EOSINOPHILES	BASOPHILES	LYMPHOCYTES	MONOCYTES	MYELOID CELLS, RETICULOCYTES, ETC.
1946										
3/ 9	62	4,200,000	13,300	8	11			81		Achromia, poikilocytosis, anisocytosis
4/27	50	2,340,000	9,000	30	8			57	5	Reticulocyte count 3.5%
5/18	57	3,110,000	4,500	36				54	10	Marked macrocytosis, anisocytosis and poikilocytosis
7/ 8	40	1,760,000	4,100	34	4			60	2	Marked poikilocytosis and anisocytosis
8/ 8	38	1,310,000	2,650	65	4			31		Red cells, macrocytic and eliptical; poikilocytosis, anisocytosis, reticulocyte count 0.3%
9/ 9	44	1,810,000	2,900	35	7			58		Reticulocyte count 7.5%
10/28	22	1,040,000	1,600	16	2			82		Marked anisocytosis and poikilocytosis
12/10	22	1,200,000	2,600	27	2	1		70		Marked achromia, anisocytosis poikilocytosis, polychromatophilia, reticulocyte count 1%
1947										
1/ 1	25	1,400,000	3,600	37	12			56	4	Achromia, polychromatophilia, anisocytosis
1/11	19	610,000	3,100	39	5			55	1	Achromia, anisocytosis, poikilocytosis, polychromatophilia

TABLE V. HEMATOLOGY (CASE 2)

DATE	COAGULATION (MIN.)	BLEEDING (MIN.)	CLOT RETR. (MIN. TO HR.)	PLATELETS	R. B. C. FRAGILITY		HEMATOCRIT (MM.)	WASSERMANN
					INITIAL HEMOLYSIS	COMPLETE HEMOLYSIS		
1946								
3/18				68,000	0.45%	0.35%		
3/25	2½	2		106,000*			21	Negative
4/27		8		34,000			28	
4/30	4	4		48,000				
5/18				80,000				
8/8	3	3		126,000*				
9/9	3	3½		40,000			17	
10/29	3	1		22,000				
11/18	2½	4		124,000*				
12/10				40,000				
12/26	5	4		50,000				
1947								
1/11				35,000				

*Following transfusions.

TABLE VI. BLOOD CHEMISTRY AND BASAL METABOLIC RATE (CASE 2)

DATE	WHOLE BLOOD			SERUM				B. M. R.
	NONPROTEIN NITROGEN (MG. %)	UREA (MG. %)	URIC ACID (MG. %)	CHOLESTEROL (MG. %)	CHOLESTEROL (EST. MG. %)	SODIUM (MG. %)	ALKALINE PHOSPHATASE (UNITS)	
3/26/46	37.5	13	3.75	119	82	325	12	plus 11

On section through the ribs, the bone marrow appears mottled with predominant yellow color. The same appearance is predominant on section through several vertebrae. Microscopic study of bone marrow shows extensive fatty changes with only occasional evidence of hemapoiesis consisting mostly of nucleated red cells.

Anatomical Diagnoses.—Aplastic anemia; petechial hemorrhages in skin, epicardium, endocardium, pleura, lungs, gastrointestinal tract; marked fatty changes in the bone marrow; fatty infiltration of the liver, limited; extensive anoxemic changes of the heart muscle with necrosis and hemorrhage; terminal thrombotic nonbacterial endocarditis, mitral valve.

Cause of death: Aplastic anemia with marked cardiac anoxia.

COMMENT

The two cases described in siblings are proved examples of aplastic anemia of the "Fanconi type." The association of pancytopenia and multiple congenital defects supports this contention. In the first case, A. W., the hemogram disclosed a constant diminution of the hemoglobin, red blood corpuscles, white blood corpuscles, platelets, and reticulocytes. The lymphocytes were constantly increased. Sternal marrow aspiration disclosed a grossly fatty marrow, with a characteristic aplastic picture of hypocellularity. In addition to the aplastic hematopoietic system, other aberrations were evident in the skin, ears, eyes, skeletal system, kidney, and adrenal. A brownish, melanin-like appearance of the skin, associated with vitiligo, "café au lait" spots, freckling, and hirsutism were observed. Deformities of both ear auricles had been partially corrected by plastic surgery. However, a marked diminution in auditory perception was evident from infancy. Congenital ptosis of both upper eyelids with microphthalmia was obvious. Ophthalmoscopic examination showed a whitish appearance of both nerve heads with a vertical, elliptical configuration. At first it was suggested that this was a pseudoneuritis due to a refractive error, rather than a papilledema, since the appearance of the eye grounds remained the same over a period of months. Histological examination proved that edema of the disc rather than pseudoneuritis was responsible for this interesting picture. Papilledema is observed at times in various types of blood dyscrasias in the absence of unrelated intracranial pathology.[12] The explanation of the mechanism is not clear. The retina and optic nerve depend upon an adequate supply of oxygen. Anoxemia due to the reduced oxygen-carrying power of the blood may be responsible for an anoxia of the tissues of the optic nerve and retina, resulting in visible papilledema. The profound anemia persisting over a period of months with frequent hemorrhagic manifestations, such as hemorrhages into the vitreous and retina, may produce terminal retinal detachment.

Skeletal abnormalities included a rudimentary right thumb, which was attached to the hand by a fold of skin. The proximal phalanx of this thumb was undeveloped and the metacarpal bone was absent. The left thumb was thinner than usual, resembling a finger, and its flexion was markedly restricted. The number of carpal centers in both wrists was reduced.

The urological malformations included absence of the right kidney and hypertrophy of the left kidney with double ureters.

The endocrine system disclosed a hypoplasia of the right adrenal gland.

In the second case, I. W., hematological examinations were not remarkable until the onset of symptoms at the age of 6 years. At this time there was a marked reduction in all elements of the hemogram, including hemoglobin, red blood cells, white blood cells, platelets, and reticulocytes. Lymphocytosis was noted on most of the examinations. A sternal marrow aspiration showed a definite aplastic picture, characterized by a grossly fatty marrow with hypoplasia of all the cellular elements.

Other abnormalities were noted in the skin, eyes, and skeletal system. Melanin-like, brownish pigmentation, freckling, and areas of vitiligo were seen on the skin. Microphthalmia, strabismus, and papilledema were obvious in this child. Skeletal abnormalities included microcephaly, a delay in the appearance of the carpal centers, and a double nucleus in the tarsal scaphoid.

Gates[13] considers this syndrome as a hereditary blood disorder with a clear familial distribution caused by recessive outcroppings. In his study on congenital defects, Murphy[14] noted a tendency for the appearance of similar malformations, particularly in the later-born siblings. He suggested the possibility of some maternal factor which might be responsible for reproductive inefficiency. His survey disclosed that in families already possessing a malformed child, the chances of producing another were approximately twenty-four times greater than the rate in the general population. Consanguinity on the maternal side, in the cases I am reporting, would suggest the possibility of a recessive hereditary factor as the etiological agent in this syndrome. However, Murphy,[14] in his study on congenital malformations, states that only ten of 553 families gave a history of consanguineous marriage. The congenital aberrations noted in these two children are probably the result of defective germ plasm or consanguinity.

Warkany[15, 16] does not agree with the attitude in the literature attributing the etiology of most congenital malformations to changes in the germ plasm. In his monograph and paper on the subject, his experiments and discussion disclose that environmental influences may frequently be responsible for these malformations. Congenital deformities in animals were produced by him and his co-workers by creating nutritional deficiencies. However, it does not necessarily follow that these results may be duplicated in the human fetus. Rubella[17] and toxoplasmosis[18] are examples of two infections which may cause congenital defects. Clifford and Weller[19] could not prevent retrolental fibroplasia from developing in premature infants' eyes by the daily administration of vitamin A orally and parenterally. These results are in contrast to those recorded by Warkany[15] in which maternal vitamin A deficiency in the rat had produced retrolental fibroplasia.

It is significant that the blood dyscrasia in these two siblings did not manifest itself until they had attained the age of 6 years. This would suggest that the germ plasm responsible for the production of the hematopoietic system was imperfect in both instances, resulting in an exhaustion phenomenon. Consequently, the pan-

On section through the ribs, the bone marrow appears mottled with predominant yellow color. The same appearance is predominant on section through several vertebrae. Microscopic study of bone marrow shows extensive fatty changes with only occasional evidence of hemapoiesis consisting mostly of nucleated red cells.

Anatomical Diagnoses.—Aplastic anemia; petechial hemorrhages in skin, epicardium, endocardium, pleura, lungs, gastrointestinal tract; marked fatty changes in the bone marrow; fatty infiltration of the liver, limited; extensive anoxemic changes of the heart muscle with necrosis and hemorrhage; terminal thrombotic nonbacterial endocarditis, mitral valve.

Cause of death: Aplastic anemia with marked cardiac anoxia.

COMMENT

The two cases described in siblings are proved examples of aplastic anemia of the "Fanconi type." The association of pancytopenia and multiple congenital defects supports this contention. In the first case, A. W., the hemogram disclosed a constant diminution of the hemoglobin, red blood corpuscles, white blood corpuscles, platelets, and reticulocytes. The lymphocytes were constantly increased. Sternal marrow aspiration disclosed a grossly fatty marrow, with a characteristic aplastic picture of hypocellularity. In addition to the aplastic hematopoietic system, other aberrations were evident in the skin, ears, eyes, skeletal system, kidney, and adrenal. A brownish, melanin-like appearance of the skin, associated with vitiligo, "café au lait" spots, freckling, and hirsutism were observed. Deformities of both ear auricles had been partially corrected by plastic surgery. However, a marked diminution in auditory perception was evident from infancy. Congenital ptosis of both upper eyelids with microphthalmia was obvious. Ophthalmoscopic examination showed a whitish appearance of both nerve heads with a vertical, elliptical configuration. At first it was suggested that this was a pseudoneuritis due to a refractive error, rather than a papilledema, since the appearance of the eye grounds remained the same over a period of months. Histological examination proved that edema of the disc rather than pseudoneuritis was responsible for this interesting picture. Papilledema is observed at times in various types of blood dyscrasias in the absence of unrelated intracranial pathology.[12] The explanation of the mechanism is not clear. The retina and optic nerve depend upon an adequate supply of oxygen. Anoxemia due to the reduced oxygen-carrying power of the blood may be responsible for an anoxia of the tissues of the optic nerve and retina, resulting in visible papilledema. The profound anemia persisting over a period of months with frequent hemorrhagic manifestations, such as hemorrhages into the vitreous and retina, may produce terminal retinal detachment.

Skeletal abnormalities included a rudimentary right thumb, which was attached to the hand by a fold of skin. The proximal phalanx of this thumb was undeveloped and the metacarpal bone was absent. The left thumb was thinner than usual, resembling a finger, and its flexion was markedly restricted. The number of carpal centers in both wrists was reduced.

The urological malformations included absence of the right kidney and hypertrophy of the left kidney with double ureters.

The endocrine system disclosed a hypoplasia of the right adrenal gland.

In the second case, I. W., hematological examinations were not remarkable until the onset of symptoms at the age of 6 years. At this time there was a marked reduction in all elements of the hemogram, including hemoglobin, red blood cells, white blood cells, platelets, and reticulocytes. Lymphocytosis was noted on most of the examinations. A sternal marrow aspiration showed a definite aplastic picture, characterized by a grossly fatty marrow with hypoplasia of all the cellular elements.

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It is significant that the blood dyscrasia in these two siblings did not manifest itself until they had attained the age of 6 years. This would suggest that the germ plasm responsible for the production of the hematopoietic system was imperfect in both instances, resulting in an exhaustion phenomenon. Consequently, the pan-

cytopenia became evident at the same chronological age in both children.

There was no history of exposure to sulfonamides, benzol, arsenobenzol, radium, x-rays, or any agent known to produce hypoplasia or aplasia of the marrow. Idiopathic, aplastic anemia may sometimes be the culmination of a familial tendency to neutropenia, anemia, or thrombopenia.[20] The family history does not reveal any such tendency in this instance.

The role of splenectomy in the treatment of aplastic anemia merits discussion. Rosenthal[21] believes that splenectomy in chronic aplastic anemia is ineffective as a curative procedure. Estren, Suess, and Dameshek[5] performed a splenectomy in their case and indicated that improvement followed this operation. However, further observation of this case is necessary before any definite conclusions are possible. Van Leeuwen's[7] and Dacie and Gilpin's[8] patients lived for three years following splenectomy. In the former instance no favorable response was noted, but temporary improvement followed in the latter.

SUMMARY

Two cases of aplastic anemia are described in siblings. The first is a classic example of the Fanconi type. The association of pancytopenia and multiple congenital defects supports this contention. In addition to the aplastic anemia, other aberrations were evident in the skin, ears, eyes, skeletal system, kidney, and adrenal. Papilledema, due to anoxemia of the optic nerve, was demonstrated clinically and at necropsy.

The second case is of special interest in connection with the first, since the onset of the aplastic anemia occurred at the same chronological age in this sibling. This child had abnormalities, including pigmentation, vitiligo, microphthalmia, strabismus, and papilledema. Skeletal malformations observed were microcephaly, a delay in the appearance of the carpal centers, and a double nucleus in the tarsal scaphoid. While this boy did not present as many of the typical features of the Fanconi type as his brother, he had sufficient abnormalities to be included in this syndrome.

The occurrence of aplastic anemia with congenital malformations in two brothers suggests that the congenital aberrations were probably the result of defective germ plasm or consanguinity.

The onset of the aplastic anemia was observed in both children at the age of 6 years. This coincidence may be due to an exhaustion phenomenon, incurred by a familial congenital constitutional defect of the marrow germ plasm. Normal hematopoietic function continued for six years until this inadequacy became manifest.

Splenectomy in the treatment of aplastic anemia has proved of limited value.

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PULMONARY HYPERTENSION IN CHILDREN DUE TO CONGENITAL HEART DISEASE

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MOST papers and discussions on the subject of hypertension have been concerned in the past with systemic arterial hypertension. Only recently have articles appeared in the literature concerning pulmonary arterial hypertension,[1, 2] and none of these have been in the pediatric literature. Edwards[3] believes that there are four basic types of pulmonary hypertension based on the etiology:

1. Normal fetal hypertension.
2. Those conditions with a disproportion between pulmonary blood flow and pulmonary vascular capacity.
   a. Those congenital heart malformations with increased pulmonary blood flow.
   b. Those conditions with intrapulmonary pathology (i.e., emphysema, cystic fibrosis, silicosis, etc.).
3. Those intra- and extracardiac conditions which produce an impaired venous return from the lungs (i.e., mitral disease, constrictive pericarditis, etc.).
4. Those congenital heart malformations with a common ventricular ejectal force in the absence of pulmonary stenosis.

It has been known for some time that fetal animals have pulmonary hypertension relative to the systemic pressure,[4] and although no measurement has been made in man it seems logical to assume that a similar situation occurs in the human fetus. This hypertension is necessary in order that oxygenated blood will flow from the pulmonary artery through the ductus arteriosus into the aorta. Barclay and associates[16] have shown that this occurs in living sheep fetuses. The right ventricle thus must supply blood to the lungs and aorta simultaneously; in effect it functions as a "systemic ventricle." In certain congenital heart conditions the right ventricle likewise becomes the "systemic ventricle,"[75] i.e., (1) coarctation of the aorta proximal to a patent ductus arteriosus; (2) persistent truncus arteriosus without pulmonary stenosis; (3) the Eisenmenger complex; (4) a single ventricle without pulmonary stenosis; (5) the Taussig-Bing complex; (6) tricuspid atresia without pulmonary stenosis.

Very few instances of pulmonary hypertension have been reported in patients with congenital heart disease other than those conditions just enumerated above. It is the purpose of this communication to call attention to the fact that pulmonary hypertension is not infrequently encountered in the more common congenital heart defects with increased pulmonary blood flow, i.e., patent ductus arteriosus, interatrial septal defect, and interventricular septal defect.

MATERIAL AND RESULTS

During the past two and one-half years, heart catheterizations have been performed on approximately 220 infants and children in our clinic for

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diagnostic purposes. From this group of patients with heterogenous congenital heart lesions, thirty-one were found to have pulmonary hypertension according to the criteria of Borden.[1] A breakdown of this group of patients according to the clinical anatomical diagnosis shows the following:

9 cases due to a patent ductus arteriosus.
9 cases due to an interventricular defect.
5 cases due to an interatrial defect.
4 cases due to an aortic-pulmonary septal defect.
3 cases with idiopathic hypertension.
1 case due to an Eisenmenger complex.

Table I shows the data obtained on the nine patients with a patent ductus arteriosus. In each of these patients the clinical and catheterization diagnosis was confirmed at the time of surgical exploration. Not all of this group of patients, however, had the typical clinical and physical findings. In fact, in most instances the heart catheterization was performed in order to clarify the diagnosis.* The systolic pulmonary artery pressure in these patients ranged from 38 to 100 mm. Hg. The left to right shunt through the patent ductus arteriosus as calculated by the Fick principle varied from 1.2 to 15.2 liters per minute. Seven of the nine patients exhibited or complained of mild to moderate cardiac disability and as stated elsewhere[6] this seemed to be related to increasing pulmonary artery pressures.

Table II shows the data obtained on the nine patients with an interventricular defect. None of these patients were operated upon. The diagnosis was based upon the clinical findings plus the existence of a left-to-right shunt in the region of the right ventricle as shown by heart catheterization. Clinically, a systolic murmur was best heard in the fourth to fifth left interspace, the pulmonary second sound was normal or accentuated, and the electrocardiogram revealed only minor changes. An overriding of the aorta such as is present in the Eisenmenger complex was believed not to be present in these patients as there was no arterial desaturation. The systolic pulmonary artery pressure in these patients ranged from 40 to 100 mm. Hg. The left-to-right shunt, in those patients where it was possible to calculate, ranged from 1.4 to 21.1 liters per minute. Six of the nine patients exhibited or complained of mild to moderate

TABLE I. PATENT DUCTUS ARTERIOSUS

PATIENT	AGE (YR.)	SEX	CARDIAC DISABILITY	CARDIAC PRESSURES		SYSTEMIC PRESSURE	SYS. FLOW IN LITERS/MIN.	PULM. FLOW IN LITERS/MIN.	LEFT-TO-RIGHT SHUNT IN LITERS/MIN.
				R. VENT.	PULM. A.				
B. B.	15	F	Moderate	100/-10	110/46	110/50/0	7.1	12.6	5.5
M. P.	18	M	None	45/0	38/12	140/25	8.0	23.2	15.2
S. B.	4	F	Moderate	50/0	48/40	100/40	3.9	7.7	3.9
C. W.	9	F	Mild	50/-5	44/26	118/78/0	5.5	16.2	10.7
L. J.	2	F	Mild	40/0	50/12	110/50/20	--	--	--
G. J.	14	F	Moderate	80/0	70/50	105/40/0	5.6	16.7	11.1
M. C.*	6	F	Mild	90/0	65/40	125/60/50	4.3	5.5	1.2
D. S.*	9	M	Moderate	80/0	80/50	106/78	5.0	9.4	4.4
J. P.	11	M	None	>50†	>50†	130/60/0	5.6	9.0	3.4

*Additional intracardiac defect remained following ligation of ductus.
†Exact values not known because of error in standardization of recording instrument.

*A more detailed discussion of these cases and the problem of diagnosis is the subject of another report.[6]

cardiac disability. Although most of these patients similarly had symptoms relative to the pulmonary hypertension, patient R. F. was a glaring exception. R. F. had the unusual situation of a systolic pressure in the pulmonary artery of 100 mm. Hg, and yet had no symptoms. This pressure was an amount equal to that obtained by a blood pressure cuff in the upper extremities. Although R. F. had no evidence of arterial desaturation at the closure of the defect. In all five of the patients the diagnosis was based on the clinical findings plus the evidence of a left-to-right shunt in the right atrium as demonstrated by heart catheterization.* In patients P. A. and S. D. no pressures were obtained from the pulmonary artery because the catheter could not be advanced through the pulmonary valve. There is no reason to expect, however, pulmonary stenosis in either of these children

TABLE II. INTERVENTRICULAR DEFECT

PATIENT	AGE (YR.)	SEX	CARDIAC DISABILITY	CARDIAC PRESSURES R. VENT.	CARDIAC PRESSURES PULM. A.	SYSTEMIC PRESSURE	SYS. FLOW IN LITERS/MIN.	PULM. FLOW IN LITERS/MIN.	LEFT-TO-RIGHT SHUNT IN LITERS/MIN.
K. K	3	F	Mild	47/-3	45/13	94/20	----	----	----
S. L.	1	F	None	50/-4	54/26	114/68	----	----	----
J. U.	8	F	Mild	55/-15	50/18	100/76	----	----	----
D. S.	7	M	None	40/8	----	98/58/30	3.0	4.4	1.4
P. S.	1	F	Moderate	45/0	60/40	90/70/60	----	----	----
P. P.	12	F	Moderate	100/0	90/75	100/80	10.5	16.6	6.1
L. G.	13	F	Mild	44/0	44/22	114/56/44	16.6	9.4	2.8
R. F.	15	M	None	100/10	100/65	100/68	5.6	26.7	21.1
J. E.	3	F	Moderate	40/10	40/30	80/50	----	----	----

TABLE III. INTERATRIAL DEFECT

PATIENT	AGE (YR.)	SEX	CARDIAC DISABILITY	CARDIAC PRESSURES R. VENT.	CARDIAC PRESSURES PULM. A.	SYSTEMIC PRESSURE	SYS. FLOW IN LITERS/MIN.	PULM. FLOW IN LITERS/MIN.	LEFT-TO-RIGHT SHUNT IN LITERS/MIN.
P. A.	5	F	Moderate	40/0	40*	100/60	--	--	--
S. D.	12	F	Moderate	120/0	120*	112/84	3.3	11.8	8.5
V. B.	1½	F	Moderate	50/10	50/38	90/65	--	--	--
L. R.	6	F	Moderate	70/0	50/30	100/60	3.2	9.2	6.0
S. J.	1½	F	Moderate	50/10	50/30	98/60	--	--	--

*Systolic pressure assumed on absence of evidence of pulmonary stenosis.

time of the heart catheterization, it could be anticipated that desaturation would occur in the future as the pressure on the right side of the heart exceeded that on the left.

Table III shows the data obtained on the five patients with an interatrial defect. Two of these patients were proved to have the condition at postmortem examination, their deaths occurring during an attempt at surgical (P. A. was shown at post mortem not to have any stenosis). One could thus assume that the systolic pressure in the pulmonary artery was equal to the systolic pressure in the right ventricle. Following such an assumption, the systolic pressure in the pulmonary artery of these patients ranged from

*A complete discussion concerning the clinical and catheterization data of these patients and those with an interventricular defect is in preparation.[7]

40 to 120 mm. Hg. Oxygen consumptions were performed only on patients S. D. and L. R. of this group. This showed that the left-to-right shunt in S. D. was 8.5 liters per minute and in L. R. 6 liters per minute. All of these patients had moderate cardiac disability; in fact, surgical closure of the defect was attempted in patients P. A. and S. J. because they were becoming severe cardiac invalids requiring hospitalization most of the time.

Table IV shows the data obtained on the four patients with an aortic-pulmonary septal defect. The diagnosis in these patients was based on (1) heart catheterization which revealed the presence of a left-to-right shunt in the region of the pulmonary artery; (2) the clinical findings of an interventricular defect (namely, a systolic murmur along with a diastolic component best heard in the third or fourth left interspace); (3) evidence of right and left ventricular hypertrophy on the electrocardiogram, and (4) x-ray examination.[6] The diagnosis was proved in patients J. H. and K. N. at the time of surgical exploration. Partial closure of the defect was done in patient J. H. Attempts at closure of the defect in patient K. N. were unsuccessful and she expired during the operation. The systolic pulmonary artery pressure in these patients ranged from 40 to 80 mm. Hg. K. N. had a left-to-right shunt of 5.1 liters per minute and J. A. had 12.1 liters per minute. Three had mild cardiac disability and one had moderate disability.

Table V shows the data obtained on three patients in whom no cause for the pulmonary hypertension could be ascertained.

TABLE IV. AORTIC-PULMONARY SEPTAL DEFECT

PATIENT	AGE (YR.)	SEX	CARDIAC DISABILITY	CARDIAC PRESSURES		SYSTEMIC PRESSURE	SYS. FLOW IN LITERS/MIN.	PULM. FLOW IN LITERS/MIN.	LEFT-TO-RIGHT SHUNT IN LITERS/MIN.
				R. VENT.	PULM. A.				
K. N.	13	F	Moderate	78/10	80/58	110/70	3.2	8.3	5.1
J. H.	6	M	Mild	40/20	40*	80/65	--	--	--
J. A.	7	F	Mild	64/20	76/60	108/64	6.8	18.9	12.1
R. O.	4	M	Mild	68/10	60/54	90/60	--	--	--

*Systolic pressure assumed on absence of evidence of pulmonary stenosis.

TABLE V. IDIOPATHIC PULMONARY HYPERTENSION

PATIENT	AGE (YR.)	SEX	CARDIAC DISABILITY	CARDIAC PRESSURES		SYSTEMIC PRESSURE
				R. VENT.	PULM. A.	
A. P.	10	F	Moderate	140/0	100/40	90/60
C. S.	7	M	None	86/0	56/24	112/70
M. L.	5	F	None	60/0	60/15	108/92

Patient A. P. was a 10-year-old female who had been mildly cyanotic since birth but had a fairly good exercise tolerance. Physical examination revealed a systolic murmur that was best heard in the second and third left interspaces, and P_2 was accentuated. The electrocardiogram had marked right axis deviation, and x-rays revealed right ventricular enlargement with prominent pulmonary vascular markings. A fluorescein arm-to-lip circulation time was thirteen seconds, a value well within the normal range.

Patient C. S. was a 7-year-old male who had been known to have a heart murmur since 1 year of age. He had never had any symptoms referrable to the cardiac system. Physical examina-

tion revealed a systolic thrill and murmur best heard in the second and third left interspaces. X-ray examination revealed no chamber enlargement of the heart; however, the pulmonary artery was moderately enlarged. A fluorescein arm-to-lip circulation time was eight seconds, a value within normal limits for the child's age.

Patient M. L. was a 5-year-old girl who had been known to have a heart murmur since 2½ years of age. She was smaller than other children her age, but had no symptoms referrable to the cardiac system. Physical examination revealed a loud systolic murmur best heard in the second left interspace and an accentuated P_2. An electrocardiogram had right axis deviation. X-ray examination revealed no chamber enlargement but the pulmonary artery was moderately prominent. The fluorescein arm-to-lip circulation time was seven seconds.

It is admitted that these three patients need to be studied more completely and perhaps the heart catheterization should be repeated. However, they are included in this report for the sake of completeness.

One additional patient was catheterized, V. D., an 11-year-old female, in whom the diagnosis of Eisenmenger complex was made. This diagnosis was based on the fact that the catheter passed into the overriding aorta. Desaturation of the arterial blood was likewise present. The pulmonary artery was not entered in this patient but as in the previous cases under similar circumstances the systolic pressure in the pulmonary artery can be assumed to be equal to the systolic pressure of the right ventricle which in this patient was 100 mm. Hg. She had moderate cardiac symptoms.

DISCUSSION

According to Borden[1] pulmonary hypertension seems to be the cause, or closely related to the cause, of the patient's symptoms in mitral heart disease. Likewise, in his patients, the degree of hypertension correlated quite closely with the severity of the symptomatology. According to Edwards[5] it is likewise apparent that the pulmonary hypertension can be an important part of the pathological physiology involved in certain of the less common congenital heart defects. It has been shown in this paper that pulmonary hypertension may occur in patients with the more common congenital heart lesions such as patent ductus arteriosus, interventricular defect, and interatrial defect. When it does occur in such patients, it is nearly always associated with mild to moderate cardiac disability. Catheterization data obtained on the few patients with the diagnoses just mentioned, but lacking in symptoms would suggest that the absence of symptoms usually is accompanied by normal pulmonary artery pressures.

With a sufficient rise in the pulmonary artery pressure in either patients with a patent ductus arteriosus or with an interventricular defect, the left-to-right shunt may become diminished or abolished with eventual reversal of blood flow. Both Chapman[8] and Douglas[9] have described such an occurrence in patients with a patent ductus arteriosus.

An important part of the problem of pulmonary hypertension is the pathological changes that occur in the pulmonary arteries and arterioles in conjunction with it. These have been well described by Chapman,[8] Parker,[10] Larrabee,[11] Edwards,[5, 12, 13] Douglas,[9] Civin,[14] and others. Presently, attempts are being made to ascertain, in the patient with mitral stenosis, the

relationship between the pathological changes present in the lungs, the pulmonary artery pressures before surgery, and the results obtained following mitral commissurotomy.[15] From this study, some evidence already exists to suggest that irreversible changes may take place that preclude relief of symptoms by commissurotomy. It has been my concern that a similar situation might prevail in certain of the patients with congenital heart disease. Accordingly, in a few patients lung biopsies were obtained during surgery or at post-mortem examination, in an attempt to make a similar correlation. Dr. Edwards has been kind enough to review these sections, and in each instance changes were found to be present. In some patients the changes were only mild, i.e., slight medial thickening of the muscular arteries and slight intimal fibrosis. However, in other cases these changes were much more severe, occasionally producing complete luminal obstruction. The follow-up on the living patients has been too short and too few in number to permit any conclusions at this time except in the case of patient B. B., a 15-year-old female with a patent ductus arteriosus and severe pulmonary hypertension (100 mm. Hg). At the time of operation she had moderate medial thickening and internal fibrosis of the pulmonary arteries, and in some instances there was severe luminal narrowing. This was accompanied clinically by moderate cardiac disability. One year following ligation of her ductus arteriosus, the pulmonary artery pressure had dropped to 40 mm. Hg as demonstrated by right heart catheterization and she was free of symptoms. More such patients need to be studied in this manner, and plans are underway to do this.

SUMMARY

1. The clinical problem of pulmonary hypertension has been presented.

2. Pulmonary hypertension occurred in some children with the more common congenital heart lesions as well as those with a "systemic right ventricle."

3. The degree of hypertension correlated quite closely with the severity of the patient's symptoms and seemed to be related to its cause.

4. Pathological changes occurred in arteries of the lungs of the children with pulmonary hypertension.

The author wishes to express his appreciation to Dr. Jesse Edwards for his help and criticism in the preparation of this manuscript and also to Drs. Richard Varco, Ivan Baronofsky, and Clarence Dennis for obtaining the lung biopsies at the time of surgery.

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RIGHT HEART CATHETERIZATION IN PATENT DUCTUS ARTERIOSUS AND AORTIC-PULMONARY SEPTAL DEFECT

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THE symptoms and clinical findings in patients with typical patent ductus arteriosus are well recognized.[1-5] That not all patients with patent ductus arteriosus have the typical clinical findings is well documented.[2] Since the poor prognosis of untreated patent ductus arteriosus and the good results of surgical intervention are fairly well-established facts,[1, 2, 5-8] it is important that all patients with this condition be recognized.

Physiological studies on patients with patent ductus arteriosus have been reported on several occasions.[1, 9-16] Such studies are not only of scientific value in order that more knowledge can be gained concerning the pathological physiology involved, but particularly with the advent of cardiac catheterization, a new tool has been added that can aid in the diagnosis of the cardiac anomaly when the patient presents *atypical* findings. The purpose of this communication is to indicate the value of cardiac catheterization in such *atypical* cases and to correlate the degree of the pathological physiology involved with clinical symptomatology.

Twenty-four patients with either a patent ductus arteriosus or an aortic-pulmonary septal defect are the subject of this report. Eight of the twenty-four patients were considered, before the studies were made, to have the typical findings of patent ductus arteriosus by physical, roentgen, and electrocardiographic examination. Sixteen patients had atypical clinical findings either by physical or roentgen examination or by electrocardiography. Of this latter group after the studies were completed, six were interpreted to have an aortic-pulmonary septal defect.*

One of the patients diagnosed by heart catheterization as having an aortic-pulmonary septal defect was proved by post-mortem examination. We are aware of no previous instance in which the diagnosis of this defect was made ante mortem. In both the typical and atypical group of patients with patent ductus arteriosus the diagnosis was confirmed at surgery in each case.

RESULTS

Typical Patent Ductus Arteriosus.—Table I shows the clinical data on the eight patients considered to have a *typical* patent ductus arteriosus. Table II contains the physiological data of these eight patients obtained by right heart catheterization. In two of them the catheter was passed through the

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*One of the six patients interpreted as having an aortic-pulmonary septal defect was proved at surgery rather to have an enormous patent ductus arteriosus.

TABLE I. TYPICAL PATENT DUCTUS ARTERIOSUS

PATIENT	AGE	SEX	MURMUR	ECG	X-RAY DIAGNOSIS	CLINICAL DIAGNOSIS
M. N.	15	F	Machinery	Normal	Normal	PDA
M. P.	18	M	Machinery	Diphasic T_1	PDA	PDA
D. J.	15	M	Machinery	Normal	PDA	PDA
L. P.	14	F	S + D 2LIS	Peaked $P_{2, 3}$	Normal	PDA
J. P.	11	M	Machinery	Normal	PDA	PDA
R. A.	10	F	Machinery	Notched P_2 1° Block	PDA	PDA
M. P.	13	F	Machinery	Normal	Normal	PDA
S. M.	6	F	S + D 2LIS	1° Block	IVD	PDA

Key for This and Similar Tables

S—Systolic
D—Diastolic
LIS—Left interspace
PDA—Patent ductus arteriosus
IVD—Interventricular defect
IAD—Interatrial defect
SAS—Subaortic stenosis
MS—Mitral stenosis
AR—Aortic regurgitation

TABLE II. TYPICAL PATENT DUCTUS ARTERIOSUS

	PRESSURE (MM. HG)				OXYGEN CONTENT (VOL. %)										
PATIENT	R.A.	R.V.	P.A.	AORTA	S.V.C.	R.A.	R.V.	P.A.	F.A.	AORTA	EST. SYST. FLOW (L/MIN.)	EST. PULM. FLOW (L/MIN.)	EST. SHUNT (L/MIN.)	SHUNT AS % L. VENTRICULAR OUTPUT	DISABILITY
M. N.	–5/–10	20/–10	16/8	–	12.3	12.6	12.1	13.3	15.6	–	6.8	7.3	0.5	7	0
M. P.	1/–4	45/0	38/12	–	–	12.3	11.5	15.2	16.7	–	8.0	23.2	15.2	66	0
D. J.	1/–3	24/0	20/10	–	13.3	11.5	13.9	14.4	17.2	–	6.3	10.1	3.8	38	0
L. P.	2/–4	20/0	–	80/40	–	10.8	11.6	–	–	19.3	–	–	–	–	+
J. P.	–	Elevated		–	12.5	12.4	12.0	14.8	–	18.7	5.6	9.0	3.4	38	0
R. A.	0/–10	25/0	35/20	–	12.7	13.1	13.2	16.1	17.9	–	–	–	–	63*	0
M. P.	1/–2	22/0	18/12	–	12.6	11.8	11.8	12.8	14.9	–	9.2	13.6	4.4	32	0
S. M.	–	15/3	15/10	–	11.3	10.8	11.3	12.4	16.1	–	3.7	5.0	1.2	25	0

Key to This and Following Tables

*Shunt as % of left ventricular output based on "X" as oxygen consumption.
– Information not obtained or unreliable.
0 No cardiac disability present.
+ Mild cardiac disability present.
++ Moderate cardiac disability present.
Values from aorta obtained by intracardiac catheter.

TABLE III. ATYPICAL PATENT DUCTUS ARTERIOSUS

PATIENT	AGE	SEX	MURMUR	ECG	X-RAY DIAGNOSIS	CLINICAL DIAGNOSIS
B. B	15	F	S 2LIS	Normal	PDA	IAD
S. B.	4	F	S + D 2LIS	Large QRS complexes	IAD	IAD
L. W.	1½	F	S 2LIS	Normal	IAD	IAD
S. H.	6	F	Machinery	RAD + 120°	PS	PDA*
C. W.	9	F	Machinery	Extrasyst.	PDA	PDA + IAD
			Machinery	Slurred QRS_1		
M. B.	7	F	Machinery	RAD + 100°	PDA	PDA + IAD
L. J.	2	F	S + D 2LIS	Normal	PDA + IAD	PDA + IAD
G. J.	14	F	S + D 2LIS	Normal	IAD	PDA + IAD
A. K.	12	F	Machinery	RAD + 110°	Normal	PDA + IAD
M. C.	6	F	S 4LIS	Peaked $T_{2,3}$	PDA + IAD	PDA + IAD

*Heart catheterization revealed PS and PDA.

TABLE IV. ATYPICAL PATENT DUCTUS ARTERIOSUS

	PRESSURE (MM. HG)				OXYGEN CONTENT (VOL. %)										
PATIENT	R.A.	R.V.	P.A.	AORTA	S.V.C.	R.A.	R.V.	P.A.	F.A.	AORTA	EST. SYST. FLOW (L/MIN.)	EST. PULM. FLOW (L/MIN.)	EST. SHUNT (L/MIN.)	SHUNT AS % L. VENTRICULAR OUTPUT	DISABILITY
B. B.	2/–4	100/–10	100/46	–	14.7	12.7	14.8	15.6	17.5	–	7.1	12.6	5.5	44	++
S. B.	4/–10	55/0	48/40	100/40	–	9.2	9.3	11.4	–	13.7	3.9	7.7	3.9	50	++
L. W.	1/–1	20/2	25/18	–	5.0	5.5	5.9	10.6	11.9	–	–	–	–	82*	++
S. H.	0/–6	80/0	28/18	120/78	10.2	10.4	10.0	11.0	–	13.3	2.6	3.4	0.8	24	0
C. W.	10/–2	50/–5	44/26	–	10.0	9.5	9.7	12.2	13.3	–	5.5	16.2	10.7	66	+
M. B.	0/–4	28/6	20/14	110/80	11.8	11.3	–	13.3	–	14.8	6.2	14.8	8.6	58	0
L. J.	–	40/0	50/12	–	10.9	10.3	10.5	13.3	–	–	–	–	–	71*	+
G. J.	9/0	80/0	70/50	–	9.0	11.7	12.2	14.9	16.5	–	5.6	16.7	11.1	67	++
A. K.	6/2	30/0	24/10	–	12.1	12.2	11.8	13.7	16.7	–	5.3	10.7	5.4	51	0
M. C.	–	90/0	65/40	–	9.6	9.8	9.9	10.6	13.8	–	4.3	5.5	1.2	22	+

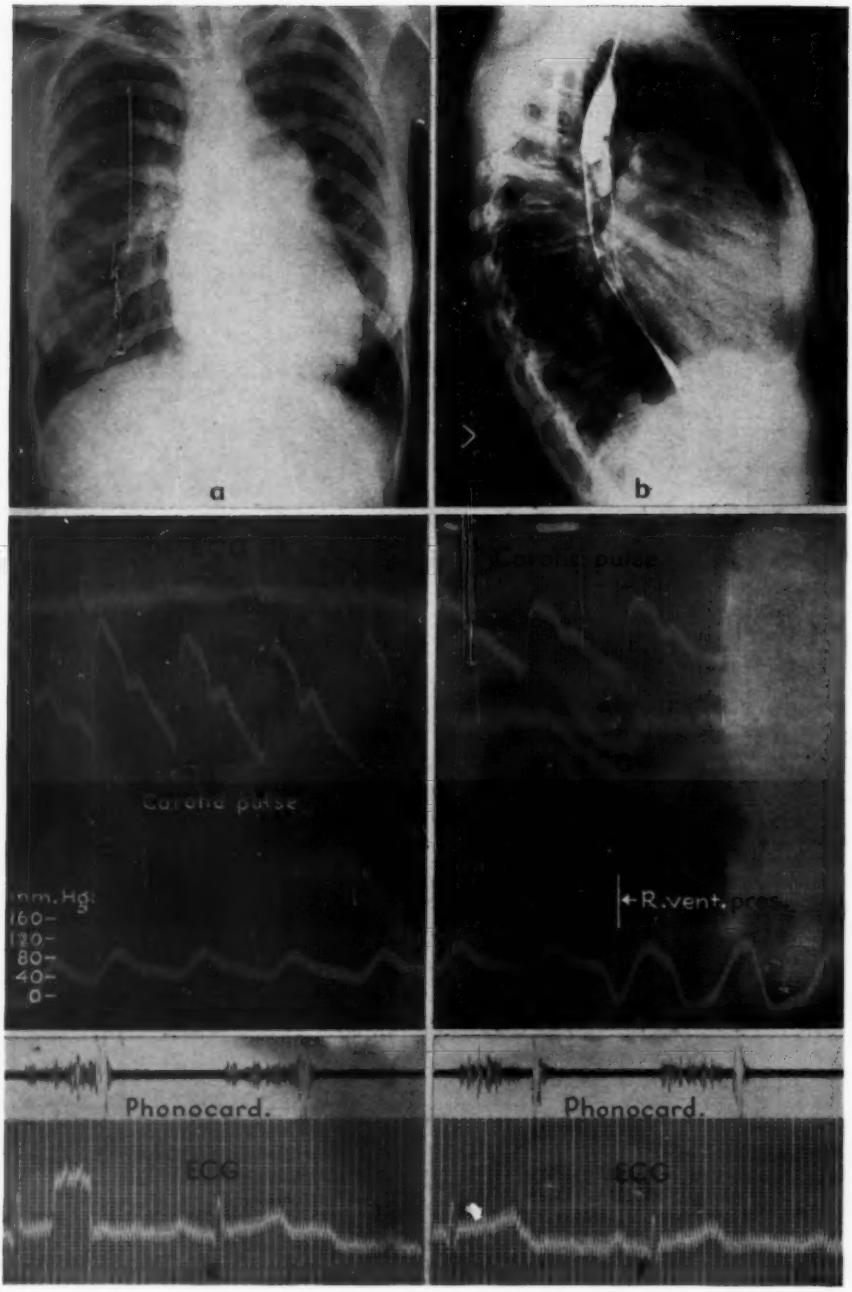

Fig. 1.—Patient B. B., 15-year-old female with atypical patent ductus arteriosus. Roentgenograms *a* and *b* show enlarged heart, prominent pulmonary artery segment, enlarged root shadows, and prominent pulmonary vascular markings. Intracardiac pressure recordings *c* and *d* show pulmonary artery and right ventricular hypertension as catheter was withdrawn through the pulmonary valve. Phonocardiograms taken in second left (*e*) and third left (*f*) interspace confirm presence of isolated systolic murmur.

ductus arteriosus into the descending aorta, thus proving the diagnosis.

Two of this group of patients, M.P. and J.P.,* had right ventricular and pulmonary artery pressures that were elevated above normal (30 mm. of mercury, systolic).

The left-to-right shunt through the ductus varied from 0.5 to 15.2 liters per minute. This represented from 7 to 66 per cent of the left ventricular output. As can be seen in Table II the amount of shunt did not correlate too well with the symptomatology; that is, some patients with large shunts had relatively few symptoms.

Atypical Patent Ductus.—Table III shows the clinical data on the ten patients other than those with aortic-pulmonary septal defects who were considered clinically not to have a typical patent ductus arteriosus. Two of these patients had only a systolic murmur audible over the left precordium and were thought clinically to have an interatrial defect. Several other patients had atypical diastolic murmurs. Six patients had abnormal electrocardiograms, three with right axis deviation. Six patients had roentgen findings not consistent with a typical patent ductus arteriosus.

Cardiac catheterization clearly demonstrated that the left-to-right shunt existed between the aorta and the pulmonary artery rather than between the atria as seen in Table IV. In three instances the catheter was passed through the ductus arteriosus thus proving the diagnosis. The phonocardiogram recordings, intracardiac pressure curves, and roentgen findings on patient B.B. can be seen in Fig. 1.

From Table IV it can be seen that the shunts varied from 0.8 to 11.1 liters per minute; this represented from 24 to 67 per cent of the left ventricular output. (Two patients had higher shunts when expressed as percentage of left ventricular output, but the absolute values were not obtained.) Seven of these ten patients had mild to moderate cardiac disability.

Aortic-Pulmonary Septal Defect.—Table V shows the clinical data on six patients who following these studies were interpreted to have an aortic-pulmonary communication or defect near the base of the heart. This diagnosis was based on the location of the murmur and the presence of a left-to-right shunt in the region of the pulmonary artery.

Only one of these patients had a machinery murmur*; the other patients had a systolic murmur either alone or in combination with a diastolic murmur best heard in the *third and fourth left interspace.* Five of the six patients had abnormal electrocardiograms consisting of right axis deviation in two and large biphasic QRS complexes in four. Three of the six patients were thought by roentgen examination to have an interatrial defect combined with mitral stenosis.

As seen in Table VI, all of the patients had a right ventricular hypertension and pulmonary artery hypertension except M.K. The shunts varied from 4.4 to 21.9 liters per minute, and the shunt expressed as per cent of the

*The exact pressures obtained in patient J. P. were not recorded in the table because of technical difficulties in standardization of the instrument.

*A patent ductus arteriosus was proved not to be present at surgical exploration and the surgeons described the murmur and thrill as originating at the base of the heart. No attempt was made to dissect out this patient's defect.

TABLE V. AORTIC-PULMONARY SEPTAL DEFECT

PATIENT	AGE	SEX	MURMUR	ECG	X-RAY DIAGNOSIS	CLINICAL DIAGNOSIS
K. N.	13	F	S + D 3LIS	Large biphasic $QRS_{2, 3}$	PDA	A-P defect
J. H.	6	M	S + D 3-4LIS	Low P_1 large $QRS_{2, 3}$	IAD + MS	IAD + MS
J. A.	7	F	S 3LIS	Large biphasic $QRS_{1, 2, 3}$	IAD + MS	IVD
D. S.*	9	M	S 3-4LIS	RAD 107°	IVD	SAS + IVD
M. K.	11	F	Machinery At base	Normal	PDA	SAS + AR
R. O.	4	M	S + D 3-4LIS	RAD large R_3	IAD + MS	IAD

*Surgical exploration revealed a patent ductus arteriosus rather than an A-P septal defect.

TABLE VI. AORTIC-PULMONARY SEPTAL DEFECT

	PRESSURE (MM. HG)				OXYGEN CONTENT (VOL. %)										
PATIENT	R.A.	R.V.	P.A.	AORTA	S.V.C.	R.A.	R.V.	P.A.	P.A.	AORTA	EST. SYST. FLOW (L/MIN.)	EST. PULM. FLOW (L/MIN.)	EST. SHUNT (L/MIN.)	SHUNT AS % L. VENTRICULAR OUTPUT	DISABILITY
K. N.	1/–2	78/10	80/58	–	10.0	12.2	13.5	14.5	17.0	–	3.2	8.3	5.1	61	++
J. H.	–1/–4	40/20	–	80/65	13.3	10.3	10.3	13.1	14.6	14.7	–	–	–	54*	0
J. A.	2/–10	64/20	76/60	–	13.9	12.0	13.8	16.2	17.5	–	6.8	18.9	12.1	64	+
D. S.*	2/–5	80/0	80/50	–	12.5	11.6	11.8	14.9	18.7	–	5.0	9.4	4.4	46	++
M. K.	–1/–3	16/0	12/10	–	11.2	11.1	11.7	12.9	13.8	–	11.0	32.9	21.9	67	0
R. O.	0/–8	68/10	60/54	–	10.2	11.4	12.7	14.5	14.9	–	–	–	–	85*	+

*Surgical exploration revealed a patent ductus arteriosus rather than an A-P septal defect.

left ventricular output varied from 46 to 85 per cent. Four of the six patients had mild to moderate cardiac disability.

In one patient, J. H., the catheter was passed through the defect, into the aorta as seen in Fig. 2, thus proving the diagnosis. The anterior position of the catheter in the lateral view showed that it had not passed through the ductus arteriosus.

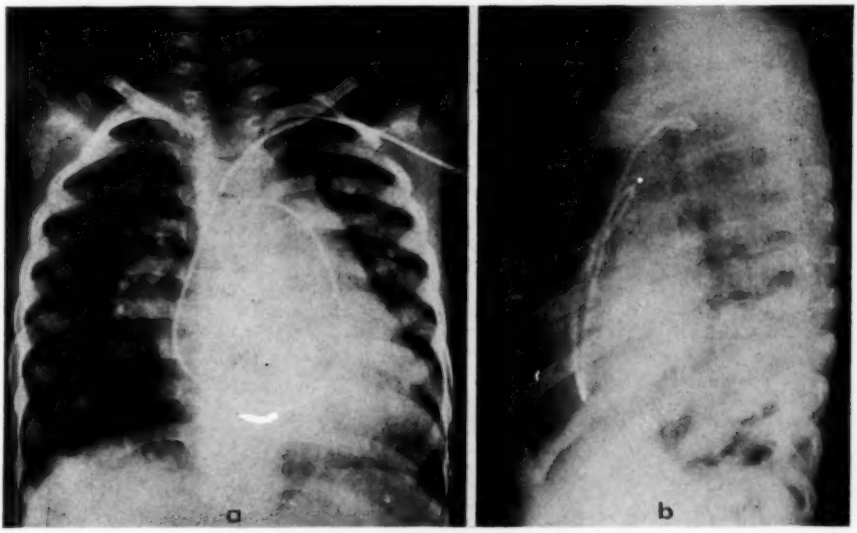

Fig. 2.—Patient J. H., 6-year-old male with aortic-pulmonary septal defect. Roentgenograms *a* and *b* show position of catheter which has passed from the pulmonary artery through the defect into the ascending aorta. The tip is near the aortic valves. Note how the catheter remains anterior in the lateral view thus showing it had not passed into a patent ductus arteriosus and then into the aorta.

Patient K. N. was suspected clinically of having an aortic-pulmonary septal defect, because of the location of the murmurs, before the heart catheterization studies were made, and as can be seen in Table VI, these studies showed the shunt to be in the region of the pulmonary artery. A surgical attempt to close the defect in this patient was unsuccessful, and she expired on the operating table. Fig. 3 shows the heart specimen illustrating the defect, and also the roentgen findings in this case.

Although following the catheterization studies patient D. S. was thought to have an aortic-pulmonary septal defect primarily because of the location of his heart murmurs, this proved not to be the case. At surgical exploration an enormous patent ductus arteriosus was found and there was no defect in the aortic-pulmonary septum region. Following ligation of the ductus, however, there remained a thrill in the region of the interventricular septum, and postoperatively there was clinical evidence that he had a residual interventricular septal defect.

Relationship of Shunt to Disability and Pulmonary Artery Pressure.—Fig. 4 shows the shunt as per cent of the left ventricular output plotted against the disability in the patients studied. It can be seen that there was

a number of patients that had rather large shunts but no cardiac disability. Those patients with mild to moderate cardiac disability (with one exception), all had sizeable shunts.

Fig. 5 shows the shunt as per cent of the left ventricular output plotted against the pulmonary artery pressure. Very large shunts were present in some patients without producing pulmonary

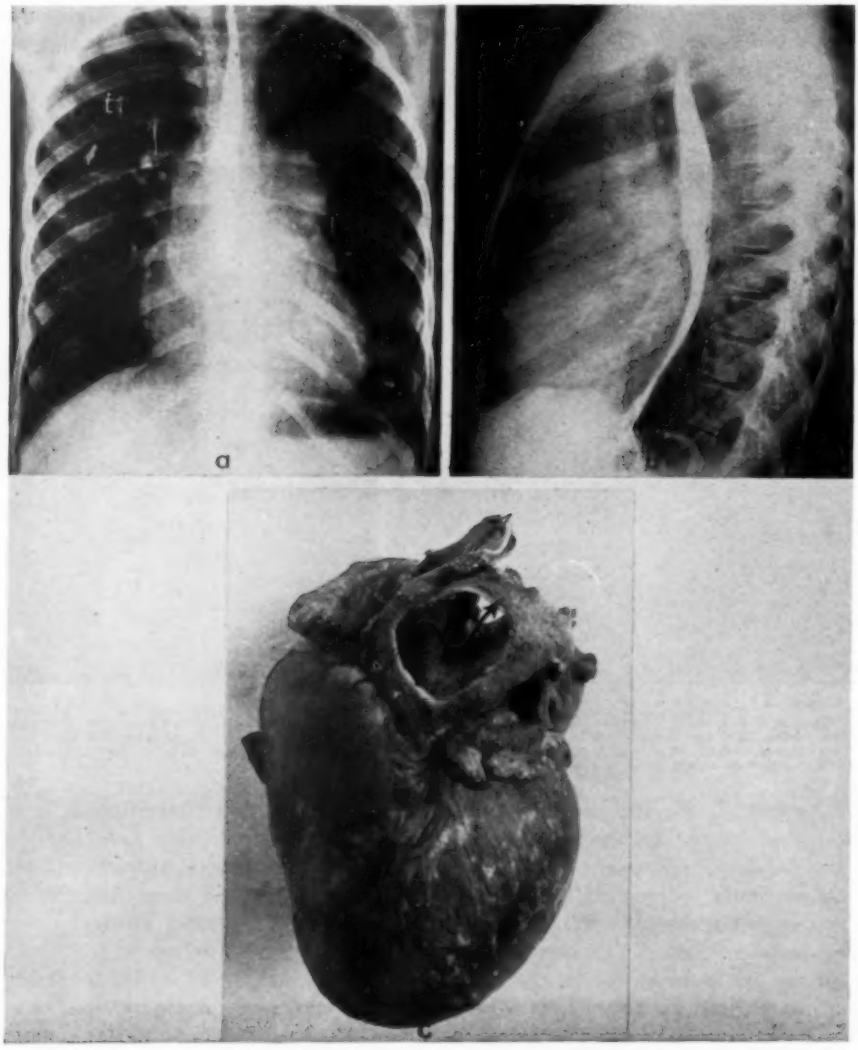

Fig. 3.—Patient K. N., 13-year-old female with aortic-pulmonary septal defect. Roentgenograms *a* and *b* show enlarged heart, prominent pulmonary artery segment, and prominent peripheral vessels. Heart specimen *c* shows defect at base of heart between aorta and pulmonary artery. Arrow shows direction of blood flow out the aorta and also through the defect into the pulmonary artery.

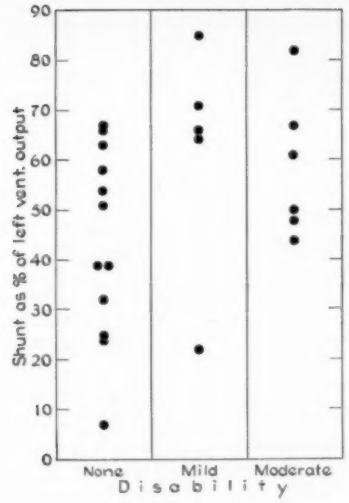

Fig. 4.

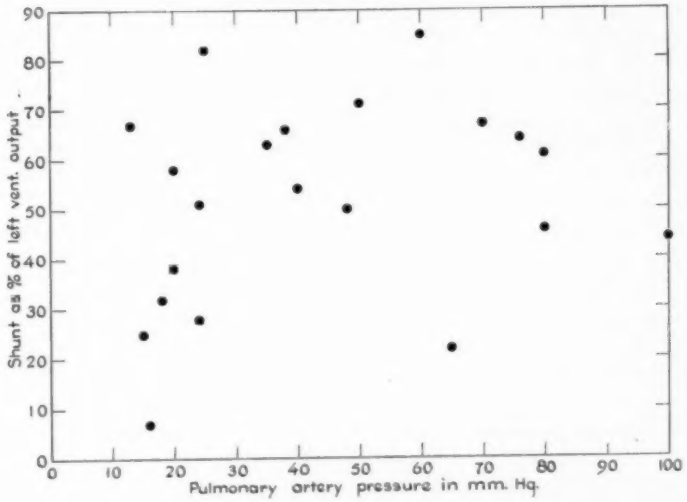

Fig. 5.

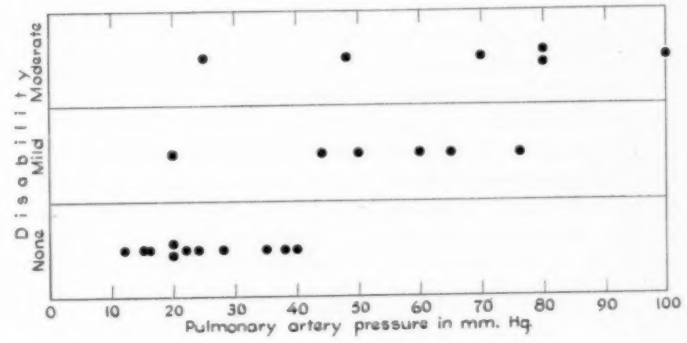

Fig. 6.

hypertension. All patients except one with pulmonary hypertension had large shunts.

Fig. 6 shows the cardiac disability plotted against the pulmonary artery pressure. It can be noted that all the patients who had no disability had relatively normal pressures, whereas most of those with disability had pulmonary hypertension.

DISCUSSION

Although right heart catheterization is of questionable clinical value in a patient who has the typical clinical findings of patent ductus arteriosus, it is of definite value in the *atypical* case. In those patients in whom the murmur, or the electrocardiogram, or the roentgenograms were atypical, the data obtained by right heart catheterization were extremely illuminating. Several patients thought to have some other defect were found by this technique to have a patent ductus arteriosus, and thus too received the benefit of surgical ligation. In several instances the diagnosis was proved before surgery by passing the catheter through the ductus arteriosus and down into the aorta.[15]

Using the heart catheterization technique our observations on pulmonary blood flow and the amount of shunt agree quite well with those of previous investigators.[1, 9, 16] Taylor and associates[16] found no consistent relationship between the size of the ductus arteriosus and the amount of shunt through it. In our studies, although some patients had large shunts with normal pulmonary artery pressures, most of the patients with elevated pressures had large shunts. Increasing cardiac disability seemed to be related to the increase in pulmonary artery pressure.

Right heart catheterization is also of value in establishing the diagnosis of an aortic-pulmonary septal defect. In some instances it is possible to pass the catheter through the defect into the aorta, thus proving the diagnosis. This can be distinguished from the situation where the catheter has passed through the ductus arteriosus into the aorta by the anterior position of the catheter in the lateral view. In other instances the diagnosis can only be presumed in those patients who have a left-to-right shunt in the region of the pulmonary artery as shown by heart catheterization and who on physical examination have a murmur with the maximum intensity in the region of the *third and fourth left interspace* or just beneath the sternum.

According to Spencer,[17] only thirteen instances of aortic-pulmonary defect have been previously reported in the literature up to 1950. Ten of the cases were from Maude Abbott's collection. Spencer added an additional case of his own in his review. Since we have collected five patients in less than two years as a result of these physiological studies, it seems probable that this defect is not as rare as is indicated from the literature.

Recently Gibson and co-workers[18] have reported four patients operated on for patent ductus arteriosus in whom no ductus was found. The murmur and thrill were described by the surgeon as coming from the base of the heart. This suggested to the authors that the patients probably had an aortic-pulmonary defect. The clinical impression was not corroborated by physiological data or post-mortem examination, however. Only one of our patients with aortic-pulmonary defects

was thought clinically to have a patent ductus arteriosus before these studies were made.

SUMMARY

1. Right heart catheterization studies on eight patients with typical patent ductus arteriosus, on eleven patients with atypical patent ductus arteriosus, and on five patients with an aortic-pulmonary defect have been presented.

2. The importance and the value of this technique as an aid to the diagnosis in the patient with atypical clinical findings has been discussed.

3. Data were presented to show that the cardiac disability was related more to the pulmonary artery pressure than to the size of the shunt.

4. Data on five patients with aortic-pulmonary defects were presented. One patient expired and at post-mortem examination, the diagnosis was confirmed. This is the first instance of such a diagnosis being made ante mortem and confirmed at autopsy reported thus far in the literature.

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CONGENITAL CIRRHOSIS OF THE LIVER ASSOCIATED WITH INFECTIOUS HEPATITIS OF PREGNANCY

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THE incidence of cirrhosis of the liver in the newborn infant is exceedingly rare. The occurrence of cirrhosis in a newborn infant of a mother with infectious hepatitis during pregnancy has not been reported previously. In the following case there is presumptive evidence that placental transfer of the virus of infectious hepatitis can occur, resulting in cirrhosis in the newborn infant.

CASE REPORT

C. J. M., a full-term white female, was born March 15, 1950, at the Providence Lying-In Hospital. Delivery was normal and birth weight was 5 pounds, 13 ounces.

Two months before term, the mother complained of fatigue and nausea. Slight jaundice was noted and persisted until time of delivery. There was no history of recent serum injection nor exposure to infectious hepatitis. The liver and spleen were not palpable. At the time of delivery her direct van den Bergh was 4.95 mg. bilirubin per hundred cubic centimeters and an indirect of 5.63 mg. bilirubin per hundred cubic centimeters. Thymol turbidity was 8.5 units and alkaline phosphatase 12.7 Bodansky units. The cholesterol was 404 mg. per hundred cubic centimeters. The mother's blood type was group A, Rh positive. One month post partum her icteric index was 17 and her serum thymol turbidity was 6. One other child was living and well.

At birth, the infant's abdomen was noted to be distended. The infant was placed in oxygen and offered sterile water. The first few feedings were retained, following which there was persisting vomiting of brown liquid. Meconium was passed in adequate amounts. At this time the infant's hemoglobin was 19.5 Gm. per hundred cubic centimeters and the red blood count 5.52 million per cubic millimeter. There were no nucleated erythrocytes. The icteric index was 32 and the stool guaiac was positive. X-rays of the abdomen revealed gas in the small bowel but no filling of the large bowel.

The infant was transferred to the Rhode Island Hospital on the second day of life. She was a well-developed, well-hydrated newborn infant with no icterus and no edema. The anterior fontanel was soft and flat. The heart and lungs were normal. The abdomen was soft and distended. A fluid wave and shifting dullness could be demonstrated. The liver edge was sharp, extending 3 cm. below the right costal margin. Because of persistent vomiting and increasing abdominal distention, an exploratory laparotomy was performed on the third day of life. The peritoneal cavity contained a large quantity of straw-colored fluid. The liver was enlarged, congested, and smooth. The gall bladder was filled

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with bile but not distended. The stomach, duodenum, and small bowel were of normal size, without evidence of obstruction. A biopsy of the liver was not done because of the necessity of extending the incision and moderate bleeding.

On the fifth day of life, jaundice was first noted. The icteric index was 25. The abdomen became progressively distended and 90 c.c. of dark orange fluid were removed by paracentesis. The specific gravity of the ascitic fluid was 1.015 and total protein was 2.5 Gm. per hundred per cubic centimeters. The red blood count, hemoglobin, and white blood count remained at normal levels. After the initial examination, stools were guaiac negative and positive for bile. Repeated examinations of the urine were within normal limits for urobilinogen but were positive for bile. Stool tryptic activity was normal. Blood Hinton was negative. The prothrombin time was 90 per cent of normal. The thymol turbidity was 1 and serum total protein was 5.2 per hundred cubic centimeters.

At 2 months of age, a punch biopsy of the liver was done. (Fig. 1.) "Sections of the needle biopsy reveal distortion of the architecture by fibroplastic proliferation. The liver cells appear to be pinched off in several foci by fibrous tissue. In one focus there is active granulation as evidenced by dilated vascular spaces with intervening fibroplastic tissue and occasional inflammatory cells. There is evidence of bile stasis, as well as of hemosiderin pigment located in the reticuloendothelial cells. There are foci of erythropoiesis."

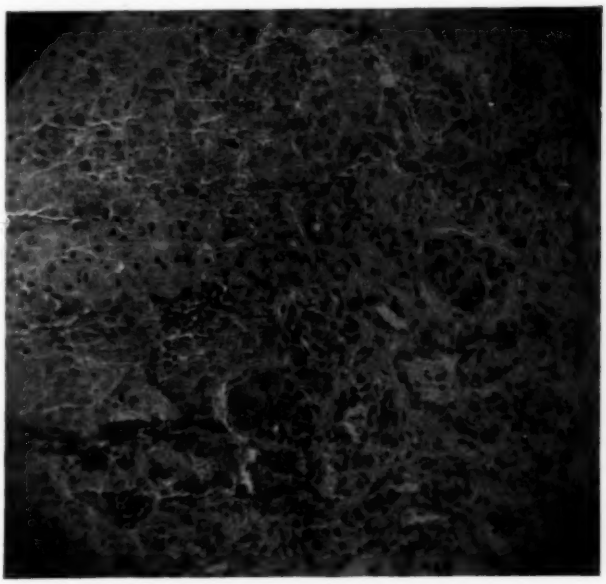

Fig. 1.—Section of liver obtained by punch biopsy.

The infant was fed a high-protein, low-fat formula with supplementary vitamins in large doses. Feedings

were taken well. However, weight gain was slow and at 5 months, weight was only 7 pounds. To relieve the abdominal distention, weekly paracenteses were necessary. The amount of ascitic fluid removed gradually increased from 500 c.c. at 3 months to as much as 1,500 c.c. at 1 year. (Fig. 2.) Jaundice was marked and gradually cleared during the fourth month. The venous pattern on the abdomen was now prominent. The liver edge was firm and nodular, extending 5 cm. below the right costal margin. At 6 months, craniotabes was noted but there was no x-ray evidence of rickets. Repeated determinations of the thymol turbidity were normal. At the age of 9 months, liver function study revealed the following: thymol turbidity 0.5, cadmium sulfate 0, thymol flocculation 0, cephalin-cholesterol flocculation 1-2 plus, total serum bilirubin 0.54 mg. per hundred cubic centimeters, and 1 minute serum bilirubin 0.08 mg. per hundred cubic centimeters.

The patient was seen Oct. 1, 1951, at the age of 18 months. Her weight was 18 pounds. She creeps and stands with support. For the last two months there has been no further accumulation of ascitic fluid. On examination she is fairly well nourished. Abdomen was much less distended with a less prominent venous pattern. Liver was enlarged three fingerbreadths below the right costal margin. Edge was firm with pea-sized nodules. Spleen reached to the iliac crest. There was no evidence of rickets. Youngster continues to be on a high-protein, low-fat diet with restricted salt.

Fig. 2.—Patient at 9 months of age, following weekly abdominal paracentesis.

DISCUSSION

Of the two major types of cirrhosis occurring during infancy, biliary cirrhosis is the more common and results from obstruction to the flow of bile. The characteristic pathology is interlobar fibrosis, bile stasis, and a chronic inflammatory process. Biliary cirrhosis is manifested clinically by obstructive jaundice. This case does not con-

form to these criteria. Portal cirrhosis or diffuse nodular cirrhosis is primarily a morphological diagnosis characterized by extensive perilobular fibrosis, infiltration of chronic inflammatory cells and focal regeneration of liver cells.[1] Causative factors include dietary deficiency, alcohol, and hepatotoxic agents. Recognized congenital forms of portal cirrhosis are hepatolenticular degeneration of Wilson, hereditary angiomatosis,[2] generalized cytomegalic inclusion disease,[3] and that following erythroblastosis fetalis. Pathological findings in this case are consistent with a portal type of cirrhosis. Since the usual causes of cirrhoses could not be demonstrated, the relationship of infectious hepatitis in the mother with cirrhosis of the liver in the infant seems significant.

Several authors have reported the occurrence of infectious hepatitis in pregnancy. Zondek and Bromberg[4] described twenty-nine cases of infectious hepatitis in pregnant women. All the newborn infants delivered at term were clinically free of liver disease. Prematurity was recognized as an important complication of maternal infectious hepatitis and accounted for the four deaths in their series. They could find no evidence of intrauterine transmission of the virus of infectious hepatitis. This was explained either on the inability of the virus to pass through the chorionic barrier or because the virus circulated in insufficient amount in the blood to induce infection. Of the four cases of infectious hepatitis in pregnancy reported by Martin and Ferguson[5] there were two deaths due to prematurity but no evidence of liver disease. Stokes[6] has demonstrated that the virus of infectious hepatitis can cross the placental barrier. Sera of infants born to mothers with infectious hepatitis were injected into human volunteers with subsequent development of hepatitis. With this evidence, infectious hepatitis can be included with other virus infections, such as measles, rubella, mumps, and chicken pox, which are known to cross the placental barrier.

SUMMARY

A case of portal cirrhosis of the newborn infant associated with maternal infectious hepatitis has been presented. The causes of cirrhosis in the newborn infant and the possible relationship of maternal infectious hepatitis and congenital cirrhosis were discussed.

Permission to report this case was granted by Dr. Robert M. Lord and Dr. Arnold Porter.

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EARLY CLAMPING OF THE UMBILICAL CORD DURING CESAREAN SECTION

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INTRODUCTION

BUDIN,[1] seventy-five years ago, noted the blood loss which a newborn infant suffers when his umbilical cord is clamped immediately following birth. Interest in the subject was revived about ten years ago when placental blood was suggested as a donor source for blood banks: DeMarsh and his colleagues[2, 3] showed significantly lower red cell counts and hemoglobin levels in infants whose cords were clamped before pulsations ceased; they estimated that such infants lost approximately 100 c.c. of blood into the placenta (25 per cent of their total blood volume) and warned against the practice. Ballentine,[4] by a different method, confirmed this amount and it has generally been accepted. No authors, however, have been able to prove any harmful effects of this "hemorrhage" on the infant except for Wilson and his colleagues[5] who demonstrated a very slight iron deficiency type of anemia at the eighth and tenth months of age.

Landau[6] has recently suggested that the high neonatal mortality of infants born by cesarean section is caused by blood loss into a placenta which has not been compressed by uterine contractions. He recommends suspension of the placenta, still attached to the infant, until cord pulsations have ceased (six to ten minutes) and suggests such a procedure avoids blood loss and fatal shock. No red cell counts or hemoglobin determinations are recorded in his paper and there is no adequate control series. Landau's procedure unavoidably complicates the obstetrician's work and requires extra handling of the infant. His ingenious theory, if incorrect, may obscure further research into the important problem of neonatal death following cesarean section. For these reasons, it seems worth while to present the following data.

MATERIAL AND METHODS

Red cell counts and hemoglobin levels were determined on twenty-eight infants born by cesarean section. Observations were made on the first, the third or fourth, and the fifth or sixth days of life. Maternal premedication consisted of atropine and Demerol. Six mothers received spinal anesthesia; the others received nitrous oxide and oxygen, with ether and/or Vinethene. The indications for section were: previous section or cephalopelvic disproportion (twenty-one), cervical stenosis (two), previous ectopic pregnancy (one), premature separation of the placenta (one), placenta previa (two), and fractured pelvis (one). Two mothers had mild uterine contractions previous to operation; in the others, labor had not begun. The twenty-eight sections form

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TABLE I. RED CELL COUNTS AND HEMOGLOBIN LEVELS OF SECTION AND CONTROL INFANTS

	1ST DAY						3RD OR 4TH DAY						5TH OR 6TH DAY					
	RBC			HB			RBC			HB			RBC			HB		
SERIES	NO.	MEAN	S.E.	NO.	MEAN	S.E.	NO.	MEAN	S.E.	NO.	MEAN	S.E.	NO.	MEAN	S.E.	NO.	MEAN	S.E.
Section (28)	26	4.84	.12	27	16.1	.29	26	4.74	.11	27	15.6	.30	27	4.69	.12	27	15.9	.32
Control (26)	25	5.42	.13	26	17.3	.27	24	5.26	.11	26	17.0	.37	24	5.00	.12	25	16.5	.28

a consecutive series in which umbilical cords were clamped as soon as possible after delivery of the infant (usually within thirty seconds). Three infants experienced mild neonatal difficulty (grunting respirations first twelve hours of life, abdominal distention, vomiting) and one infant, suffering from marked atelectasis, died on the second day of life. The remainder of the study series did well during the hospital stay.

Red cell counts and hemoglobin levels were similarly determined on a control series of twenty-six infants who were delivered uneventfully by the vaginal route. Maternal premedication consisted of Demerol and occasionally sodium pentobarbital. One mother had caudal anesthesia; the others received nitrous oxide, oxygen, and ether. All umbilical cords were clamped as soon as possible after delivery. In general, each time a section birth in the series occurred, the next available normal vaginal birth, where the cord was clamped immediately, was selected as a control. All these infants progressed normally during their hospital stay.

All infants were delivered at the same hospital but by several obstetricians. All counts and hemoglobin determinations were made by the same technician, using Bard-Parker (calibrated) blood diluting pipettes, a Spencer-Neubauer blood counting chamber (N.B.S. 1948) and a Haden-Hausser hemoglobinometer. Data regarding neonatal jaundice, maternal hemoglobin at term, and birth weights were recorded and are discussed below.

RESULTS

Table I shows means of the red cell counts and hemoglobin levels of the twenty-eight section infants and the twenty-six control infants on their first, third or fourth and fifth or sixth days of life. Means are given with their standard errors. Because an occasional determination was missed, the number of readings on which each mean is based is supplied. There is a slight general trend toward lower counts and hemoglobin levels in both series with increasing age of the infant; it is more evident in the control series. The red cell counts and hemoglobin levels of the section infants are significantly lower than those of the control infants when figures for the same day are compared (C.R. — >2), except for the mean hemoglobin levels of the fifth and sixth day which do not differ significantly (C.R. — 1.6).* The counts and hemoglobin levels of two of the section infants with neonatal difficulty (vomiting, abdominal distention) and the single (first day) count and level of the section infant who expired did not differ from the remainder of the study series. The section infant with grunting respirations, however, showed lower counts and levels (3.55-14.2; 4.15-15.2; 3.30-12.2).

TABLE II. OBSERVED JAUNDICE IN SECTION AND CONTROL INFANTS

	SECTION		CONTROL	
JAUNDICE	NO.	%	NO.	%
None	19	68.0	15	57.8
Mild	5	17.8	6	23.0
Marked	4	14.2	5	19.2
Total	28	100.0	26	100.0

Table II gives data on jaundice in the two series. No attempt was made to record the duration of observable jaundice and merely its degree, mild

*C.R. = $\frac{\text{Difference of Means}}{\text{Standard error of difference of means}}$

or marked, is noted here. The table shows that slightly more control infants (42.2 per cent) than section infants (32.0 per cent) were jaundiced. The difference is not significant.

Table III gives third day means of the red cell counts and hemoglobin levels of infants who are classified according to their mothers' (Sahli) hemoglobin readings, where the latter were available. Although there is a trend toward higher values in the infants whose mothers had higher hemoglobin values, the distribution of the two series of mothers among the three hemoglobin categories is fairly similar.

TABLE III. MOTHERS' HEMOGLOBIN LEVELS AT TERM WITH THIRD DAY RED CELL COUNTS AND HEMOGLOBIN LEVELS OF THEIR BABIES

MATERNAL HB (SAHLI-%)	NO. MOTHERS		PER CENT MOTHERS		INFANT RBC (MEAN)		INFANT HB (MEAN)	
	SECTION	CONTROL	SECTION	CONTROL	SECTION	CONTROL	SECTION	CONTROL
<70	7	6	25.0	25.0	4.66 (6)*	4.85 (6)	15.0 (7)	16.8 (6)
70-79	15	10	53.5	41.6	4.74 (15)	5.31 (9)	15.8 (15)	17.3 (10)
>79	6	8	21.5	33.4	5.02 (4)	5.45 (8)	15.8 (5)	17.4 (8)

*Number of determinations.

Table IV gives means of the red cell counts and hemoglobin levels of the infants according to birth weight categories. The total number and percentage of infants in each weight class are presented but not all of these infants had red counts and/or hemoglobin levels determined on each day (Table I). There were four (14.3 per cent) premature infants (birth weight less than 2,500 grams) in the section series and none in the control series. Although there is a slight and irregular trend for the smaller infants to have lower red counts and hemoglobin levels, the distribution of the two series among the weight categories is similar except for the premature infants in the study series.

DISCUSSION

The estimated blood loss of 100 c.c. which the vaginally born infant suffers when his cord is clamped immediately following birth[3, 4] is not fully revealed in his red count and hemoglobin level when these are compared with those of an infant whose cord is clamped late[2]; it may be assumed that his contracting spleen spills out its reservoir of red cells to compensate. The infant with a late clamped cord, furthermore, shows a larger drop in red count and hemoglobin during his first week of life[2] and this hemolysis is reflected in the fact that he is more frequently jaundiced.[2, 7] This suggests that he has no immediate need for the extra red cells he has acquired from his cord and placenta. When it is recalled, furthermore, that the lungs of the infant at birth increase his vascular reservoir by only 5 per cent and he loses perhaps four to five times as much blood space when his cord is clamped,[8] it is not unreasonable to suppose that a placental loss of 25 per cent of his *total* blood volume at term may relieve him of a plethora of blood.

Two series of infants have been presented who seem comparable except that one group was born by cesarean section and one group by the vaginal route. The umbilical cords in both series were clamped immediately after

TABLE IV. RED CELL COUNTS AND HEMOGLOBIN LEVELS OF INFANTS ACCORDING TO BIRTH WEIGHT CATEGORIES

BIRTH WEIGHT (GM.)	NO. CASES		PER CENT CASES		1ST DAY				3RD OR 4TH DAY				5TH OR 6TH DAY			
					SECTION		CONTROL		SECTION		CONTROL		SECTION		CONTROL	
	SECT.	CONT.	SECT.	CONT.	RBC	HB	RBC	HB	RBC	HB	RBC	HB	RBC	HB	RBC	HB
<2,500	4	0	14.3	0.0	4.46	15.2	---	---	4.46	15.9	---	---	4.68	16.1	---	---
2,500-3,000	7	9	25.0	34.7	5.06	15.9	5.44	17.3	4.59	15.0	5.20	16.8	4.29	15.1	4.86	16.5
3,001-3,500	13	12	46.4	46.1	4.79	16.4	5.54	17.4	4.82	15.5	5.41	17.1	4.80	16.1	5.10	16.4
>3,500	4	5	14.3	19.2	4.99	16.3	5.06	17.3	4.99	16.5	4.99	17.4	4.91	16.3	5.16	16.4

delivery of the infants. The red cell counts and hemoglobin levels, as observed through the first five or six days of life, are very slightly lower in the section series, the difference just achieving statistical significance. It is difficult to believe, however, that this deficiency is a critical or even minor hazard for these babies. The vaginally born infants, with their slight neonatal excess of blood, showed a greater fall of red cell and hemoglobin values in their first week until their fifth- or sixth-day readings approached those of the section infants. This suggests that these infants had no urgent need for their extra blood. Plasma protein levels were not determined and the section infants may have suffered some loss of globulin, including prothrombin, into their placentas. They showed, however, no signs of hemorrhagic disease. Plasma volume was not determined but DeMarsh and his colleagues[3] have shown quite convincingly that the newborn infant, born by the vaginal route with immediate clamping of the cord, adjusts his plasma volume within 15 to 180 minutes to equal that of the infant whose cord is clamped after pulsations cease.

It is possible that early clamping of the cord of a premature infant born by cesarean section may cause him some inconvenience, since he has a relatively larger placental circulation.[2] It is probable, also, that the iron loss which the infant sustains with early clamping may result in a slight anemia later in life.[5] The data presented here, however, do not substantiate Landau's theory[6] that immediate clamping of the umbilical cord during cesarean section may result in extensive blood loss and fatal shock.

The picture of respiratory distress, cyanosis and costal retraction, appearing several hours after cesarean birth and ending frequently in convulsions and neonatal death, has been associated with the aspiration of amniotic fluid and hyalin membrane formation: Intratracheal suction seems to reduce the incidence of this syndrome[9] but it has not been universally lifesaving. The picture has also been associated with the ingestion and subsequent regurgitation and aspiration of excessive amounts of amniotic fluid: Gastric suction seems to be a partial prophylactic for the condition[10] but again it has only partially resolved the problem. The complete explanation of the neonatal mortality which follows cesarean section and approaches 10 per cent in many series is still to be discovered. Landau's theory does not seem entirely tenable. In particular, it must not discourage further investigation into this important and complex problem.

SUMMARY

1. Red cell counts and hemoglobin levels were determined in twenty-eight infants, born by cesarean section, whose cords were clamped immediately after delivery of the infant. Observations were made on the first, the third or fourth, and the fifth or sixth days of life. Counts and levels were similarly determined on a control series of twenty-six infants, born uneventfully by the vaginal route, whose cords were also clamped immediately.

2. The red cell counts and hemoglobin levels of the section infants were slightly lower than those of the control infants (just achieving statistical significance) when figures for the same day were compared.

3. The control infants, with their slight neonatal excess of blood, showed a greater fall of red cell and hemoglobin values in their first week until their fifth- and sixth-day readings approached those of the section infants.

4. The control infants showed a greater incidence of jaundice.

5. The failure of red cell counts and hemoglobin levels to reflect the section infant's blood loss when his cord is clamped immediately suggests that his contracting spleen compensates for any deficit, since it is known that his plasma volume is usually corrected within a few minutes.

6. Evidence of greater hemolysis of the control infant's neonatal excess of red cells, and realization that the newborn infant has a considerably smaller vascular bed than the fetus at term, suggests that a placental blood loss, caused by immediate clamping of the umbilical cord, may relieve the infant of a plethora of blood.

7. The data presented here do not substantiate the theory that immediate clamping of the umbilical cord during cesarean section results in critical blood loss or fatal shock.

The authors express their appreciation to Miss Esther E. Graff who determined the red cell counts and hemoglobin levels.

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ACUTE POLIOMYELITIS

Differential Diagnosis of 409 Revised Diagnoses

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THE diagnosis of acute anterior poliomyelitis is, at best, only presumptive. At present, there is available no practical laboratory test to confirm the diagnosis. Isolation of the virus from nasopharyngeal secretions and stools of patients with poliomyelitis is possible but is impractical. Complement fixation tests have not been perfected. It, therefore, remains for the clinician to make the diagnosis.

Early recognition of the disease is essential if isolation measures are to be effective. The disease appears to be one of the most widespread, highly communicable, generalized infections of childhood. It is estimated by Jungeblut[1] that the disease is extraneural in 90 per cent of the cases. Epidemiologically it is important to acknowledge the presence of poliomyelitis in a community so that other individuals who become ill may be observed closely for the early signs of central nervous symptoms. It is probable that early diagnosis and isolation of the patient with acute anterior poliomyelitis not only aids in preventing further transmission of the disease but makes possible a better prognosis for the patient. Physical activity in the early stages of the illness tends to result in more extensive and more severe paralysis.[2]

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The early symptoms of poliomyelitis are nonspecific. Headache, fever, sore throat, diarrhea, vomiting, and malaise may be the cardinal complaints. These symptoms are also present in many other febrile illnesses. Examination of the cerebrospinal fluid is helpful but is not diagnostic. The diagnosis of poliomyelitis is usually made when a patient has headache, fever, increased nuchal resistance, spasm or tightness of the back and hamstring muscles, accompanied by a spinal fluid lymphocytic pleocytosis and/or lower motor neuron (flaccid) paralysis. These findings are more significant when they occur in the poliomyelitis season.

PLAN OF THE STUDY

In the ten years from 1940 to 1949, inclusive, 1,420 patients were admitted to the poliomyelitis wards of the Philadelphia Hospital for Contagious Diseases. The diagnosis was confirmed in 1,011 patients, and in 409 (28.9 per cent) of the patients the diagnosis was revised, after clinical and laboratory evaluation.

The 409 cases were reviewed, and follow-up histories were obtained from their families, from their physicians, and from hospitals. The histories included reports of the physical examinations during office or clinic visits, operations, roentgenograms, and, in some cases, autopsies. The final diag-

TABLE I. CENTRAL NERVOUS SYSTEM DISEASES

CLASSIFICATION			NUMBER OF CASES
I. Infectious and Postinfectious States			72
(a) Bacterial meningitis		32	
Meningococcic meningitis	15		
Influenzal meningitis	5		
Tuberculous meningitis	4		
Etiology undetermined	8		
(b) Acute meningoencephalitis		2	
Postrabies vaccination	1		
Postrubeola	1		
(c) Acute meningoencephalomyelitis		9	
Postrubeola	1		
Etiology not determined	8		
(d) Guillain-Barré syndrome		13	
(e) Acute disseminating encephalomyelitis		4	
(f) Acute infectious neuromyelitis optica		1	
(g) Syphilis of the central nervous system		7	
Congenital neurovascular syphilis	1		
Meningovascular syphilis	1		
Tabes dorsalis	4		
Paresis	1		
(h) Transverse myelitis—postinfectious		2	
(i) Brain abscess		2	
II. Tumors (Primary or Metastatic)			7
(a) Neuroblastoma with cerebral metastases		2	
(b) Intramedullary ependymoma		1	
(c) Medullary glioma		1	
(d) Spinal cord tumor—etiology undetermined		1	
(e) Ependymoma of cauda equina		1	
(f) Cervical intramedullary tumor		1	
III. Toxic and Metabolic Disorders			13
(a) Postconvulsive state (febrile convulsion)		6	
(b) Lead encephalopathy		2	
(c) Tetanus		2	
(d) Acute porphyria		1	
(e) Tick paralysis		1	
(f) Diabetes mellitus—acidosis		1	
IV. Congenital Diseases			6
(a) Mental retardation		2	
(b) Cerebral palsy		1	
(c) Kernicterus		1	
(d) General cerebral aplasia		1	
(e) Hydrocephalus		1	
V. Vascular Diseases			12
(a) Cerebral hemorrhage (with hypertensive cardiovascular disease)		4	
(b) Ruptured congenital aneurysm		3	
(c) Cerebral vascular thrombosis (due to arteriosclerotic vascular disease)		2	
(d) Cerebral embolism (due to bacterial endocarditis)		1	
(e) Sickle-cell encephalopathy		1	
(f) Thrombosis of anterior spinal artery		1	
VI. Traumatic Brain Injury			3
(a) Cerebral concussion		2	
(b) Massive intracranial hemorrhage		1	
	Grand total		113 cases

nosis of each of these patients was then considered in light of our records and of those obtained by the follow-up study.

A classification of the various diseases of the revised cases was prepared. The symptoms leading to the consideration of poliomyelitis were used as a basis for the classification, rather than the organ or system of the body usually given as the category in which the disease belongs. For instance, rheumatic fever was placed under arthritis in the musculoskeletal diseases because joint pain was the presenting symptom in all of our cases of rheumatic fever. The group headings include:

1. Central nervous system diseases.
2. Peripheral nerve diseases.
3. Psychogenic disorders.
4. Respiratory diseases.
5. Musculoskeletal diseases.
6. Gastrointestinal diseases.
7. Genitourinary diseases.
8. Diseases of the skin and allied structures.
9. Generalized, acute febrile diseases.
10. Diagnosis not determined.
11. Well child.

It is the object of this paper to study the patients who had symptoms suggesting poliomyelitis but who later were found to have another disease. This was done in order to obtain information which might be helpful in the differential diagnosis.

DISCUSSION

1. *Central Nervous System Diseases* (Table I).—One hundred thirteen patients (27.8 per cent) of the revised cases had symptoms referable to the central nervous system. Infectious and postinfectious states constituted 63.7 per cent of the central nervous system diseases. *Bacterial meningitis* was the disease in this group most often confused with poliomyelitis. The etiological agent in fifteen of the cases was *Neisseria intracellularis,* in five *Hemophilus influenzae,* and in four *Mycobacterium tuberculosis.* In eight cases the organism was not isolated.

Early diagnosis of meningitis is essential because of the availability of definitive therapy. Headache, lethargy, and nuchal rigidity are seen in both poliomyelitis and meningitis. In infants there is frequently an absence of Kernig's and Brudzinski's signs. A bulging fontanel may be the only abnormal physical finding. Brainerd[3] and Pollock and associates[4] feel that the greater degree of nuchal rigidity may be helpful in differentiating meningitis from poliomyelitis or viral encephalitides. The degree of nuchal rigidity was too variable, in our observations, to rely upon this sign for the differential diagnosis. All our cases of meningococcic meningitis had petechiae in addition to the symptoms and signs indicating meningeal irritation.

Headache, lethargy, and nuchal rigidity are indications for a diagnostic lumbar puncture. In bacterial meningitis the glucose values are usually decreased, but are normal in viral infections. The protein level may be elevated in tuberculous meningitis but is usually normal in the other types of bacterial meningitis. Viral infections of the central nervous system produce increased values, as a rule. Ford and collaborators,[5] in an examination of thirty-one patients, found that the highest spinal fluid protein levels occurred by the fourteenth day of disease in poliomyelitis. The range was from 15 to 250 mg. per cent.

The chloride level of the cerebrospinal fluid in tuberculous meningitis,

early in the disease, may be normal, but is reduced as the infectious process progresses.

The bacterial meningitides, generally, show cerebrospinal fluid cell counts that are much higher than those found in the viral encephalitides and poliomyelitis. With the exception of tuberculous meningitis in which the lymphocyte or round cell predominates in the spinal fluid, bacterial meningitides exhibit a polymorphonuclear pleocytosis. In poliomyelitis and encephalitis due to viral agents, the pleocytosis may be predominantly polymorphonuclear in the very early stages but it soon becomes lymphocytic. The total spinal fluid cell count in the viral diseases and in tuberculous meningitis is usually between 20 and 200 per cubic millimeter. Occasionally, no cells may be seen in poliomyelitis even after repeated examinations of the spinal fluid. This finding does not necessarily rule out poliomyelitis, especially when accompanied by the typical clinical physical findings. At times, an early spinal fluid examination in poliomyelitis or encephalitis may reveal between 500 and 1,500 cells per millimeter[3] with a predominence of polymorphonuclear leucocytes. In some of our cases, with this picture, paralysis of muscle groups was not apparent until between the fourth and fourteenth days after the initial spinal fluid examination. A spinal fluid examination, five to seven days later, revealed the expected lymphocytic pleocytosis and elevated protein. These patients should be treated with antibiotic agents during the period of observation. The isolation of pathogenic bacteria from the spinal fluid by smear or culture obviously is against the diagnosis of poliomyelitis.

Meningoencephalitis or *meningoencephalomyelitis,* other than poliomyelitis, was diagnosed in eleven of our patients. One of the patients was an 11-year-old boy who had had a course of fourteen daily injections of rabies vaccine because of a dog bite. He exhibited fever, nuchal rigidity, and a lymphocytic pleocytosis. He had an uneventful course and recovered in one week. Others have reported severe encephalitis or myelitis after rabies vaccination,[6, 7] as well as after smallpox vaccination.[8] Both of these diseases are thought to be allergic in nature. Where there is a history of vaccination nine to fourteen days prior to the onset of symptoms involving the central nervous system, the diagnosis of postvaccinal encephalitis must be considered very strongly, especially if the illness occurs out of the poliomyelitis season. The spinal fluid examination is not helpful in differentiating between poliomyelitis and postvaccinal encephalitis or other virus infections of the central nervous system.

The history of recent infection with varicella, rubella, rubeola, or parotitis, in a patient with *meningoencephalitis* or *meningoencephalomyelitis,* aids in the differential diagnosis. Encephalitis due to the mumps virus may occur without clinical evidence of parotitis.[9] Two of our patients had measles encephalitis, and eight patients had a *meningoencephalomyelitis* of an undetermined etiology. Serum virus complement fixation tests were negative. The Virus Diagnostic Laboratory, Children's Hospital of Philadelphia, has performed complement fixation tests on all of our patients admitted since 1948 who exhibited signs

of meningeal irritation and in whom a positive diagnosis could not be made by the usual laboratory tests or by clinical findings. The central nervous system diseases, which may be differentiated by complement fixation tests, include: St. Louis encephalitis, lymphocytic choriomeningitis, Eastern and Western equine encephalitis, mumps meningoencephalitis, and influenza.

Meningitic poliomyelitis closely resembles other meningoencephalitic diseases. In the absence of a specific diagnostic laboratory test, a correct diagnosis of poliomyelitis is not possible. Poliomyelitis is unlikely when the illness occurs in the interepidemic periods and in the absence of paralytic poliomyelitis in the community.

The diagnosis of *Guillain-Barré* syndrome was made in thirteen of our patients. This disease has been described under many synonyms[10] and is most frequently referred to as acute radiculomyelitis. Whether or not the Guillain-Barré syndrome is the same disease as Landry's paralysis is not agreed. Landry's type of ascending paralysis is seen in a number of neurological conditions with various etiological factors. For this reason some authors feel that it is not a disease entity but is a nonspecific syndrome of paralysis which is often associated with the clinical picture presented by Guillain and Barré. The prognosis in Guillain-Barré syndrome is usually good. Recovery of paralysis is more rapid and more complete than paralysis in poliomyelitis. Death may occur from respiratory failure or pneumonia.[11]

The clinical picture of Guillain-Barré syndrome is one of an ascending, symmetrical, flaccid paralysis more severe in the proximal muscles and frequently occurring several days after an upper respiratory infection. There may be hyperesthesias, numbness of extremities, some degree of loss of vibratory and/or pain sensation. The presence of nuchal rigidity is denied by some authors. Increased nuchal resistance was noted in eight of thirteen of our cases. Bulbar palsies were present in seven cases. Paresthesias were commonly present in all our patients. There were three deaths in the group, all of whom had cranial nerve involvement. Two of the fatal cases had paralysis of respiratory muscles.

The significant laboratory finding is the albumino-cytologic dissociation of the cerebrospinal fluid. The protein values of our cases ranged from 132 mg. per cent to 855 mg. per cent and the average spinal fluid cell count was 7 cells.

Four patients who became ill out of the poliomyelitis season had acute *encephalomyelitis disseminata.* These patients had upper respiratory infections about a week before the onset of weakness. Heaviness in the extremities appeared early and was followed by a slowly progressive, generalized paresis. None of these patients had an ascending paralysis. One patient had involvement of the twelfth cranial nerve, and respiratory paralysis. Another had lateral nystagmus. All the patients showed decreased to absent deep tendon reflexes, nuchal rigidity, and flaccid paralysis of all the extremities. Sensory changes were found in one patient. Muscle pain was a complaint in another. Cerebrospinal fluid findings included protein values between 25 and 52 mg. per cent, and cell counts within normal limits. Three of the patients recovered completely

and remained well. One patient died from respiratory failure; the autopsy showed edema and congestion of the brain.

Acute neuromyelitis optica was diagnosed in one case. The patient was a 5-year-old child whose history and physical findings, in addition to optic atrophy, were essentially the same as those in the four patients with acute encephalomyelitis disseminata. Since the first episode four years ago, there have been several remissions and exacerbations of symptoms.

Syphilis of the central nervous system was mistaken for poliomyelitis in seven of the admissions. One of these patients was an 8-year-old female with congenital syphilis with a history of personality changes for four months. She had signs of upper motor neuron disease, with spastic paralysis of the right arm and leg with increased deep tendon reflexes, bilateral positive Babinski's and ankle clonus. The blood and cerebrospinal fluid Wassermanns were strongly positive and the spinal fluid colloidal gold curve was paretic in type.

Four cases of meningovascular syphilis in adults, one case of paresis, and one case of tabes dorsalis were seen. These patients had strongly positive blood and spinal fluid Wassermann tests. The cerebrospinal fluid findings included increased cell counts, increased protein values, and colloidal gold curves of the paretic type.

The clinical picture of syphilis of the central nervous system may vary from mental confusion and upper motor neuron symptoms in those patients with cerebral disease, to lower motor neuron symptoms in patients with, principally, spinal cord involvement. Argyll Robertson pupils, a positive Romberg sign, positive blood and spinal fluid findings aid in establishing the diagnosis. The onset of central nervous system syphilis is usually less acute than the onset of poliomyelitis.

Acute transverse myelitis developed in two patients following an upper respiratory infection. Numbness, tingling, and pain in the legs or arms, depending upon the level of the spinal cord involvement, are prominent symptoms. In the early stages the paralysis is flaccid and deep tendon reflexes are absent. Later, the picture is one of pyramidal tract involvement with spastic paralysis and increased deep tendon reflexes. Positive Babinski sign, ankle clonus, and impaired sensation are typical findings. Bladder paralysis and paralytic ileus may be present. The cerebrospinal fluid findings may be similar to those of poliomyelitis. Acute transverse myelitis is the result of inflammatory processes, emboli, or thrombi of the blood vessels of the spinal cord.[12] It may follow or occur during the course of an acute infectious process and may be associated with a widespread disseminating central nervous system disease (encephalomyelitis), or it may be limited to a single area of the spinal cord.

Brain abscess was found in two patients who had findings suggestive of early poliomyelitis. The symptoms are those of an inflammatory brain lesion and the course tends to be septic. Motor weaknesses, when present, are upper motor neuron in type. Evidence of meningeal irritation is usually absent unless there has been a rupture of the abscess into the subarachnoid space. The sensorium is frequently clouded and headache may be a prominent symptom. Aphasia is sometimes seen. Spinal fluid pressure and spinal

fluid cells are usually increased in number. The low-grade lymphocytic pleocytosis is probably due to local meningeal irritation.[12] The focus of infection may be the ears, nose, or mastoid. A metastatic spread from an infection in the lungs, heart, or bones may be seen.

The diagnosis of brain abscess may be difficult in the absence of a recognizable focus of infection. However, the disease should offer little difficulty in differentiating it from poliomyelitis because the findings indicate pyramidal tract involvement.

Tumors of the central nervous system were found in seven patients admitted during the study period. Two of the patients had metastatic brain lesions from *neuroblastomas.* The presenting symptoms were those of central nervous system disease. The diagnosis of brain tumor is difficult in the early stages but it should not be confused with a lower motor neuron disease such as poliomyelitis. Choked discs are claimed to be present in about 90 per cent of cases.[13] According to the experience of two of us (A. S. and A. T.), choked discs are frequently absent in patients with brain tumors, and their presence undoubtedly depends on the location of the lesion. The disease is usually slow in onset, except in gliomas, with progressively severe headache and dizziness. Two of our patients were ill for less than ten days. Paralysis is spastic in type, although it may be flaccid early, and frequently involves an arm and leg on the same side. Fever is not a prominent finding. The spinal fluid pressure is elevated and the protein level is increased. Cerebral lesions may cause unilateral flaccid or hypotonic paralysis including mild weakness of the lower side of the face, with wasting in the muscles usually in the hands and shoulders but with sensory disturbances including astereognosis, and vasomotor changes (parieto-motor area involvement).[14] One of our patients was thought at first to have the Guillain-Barré syndrome because of a short prodromal period, a progressive, symmetrical, flaccid paralysis, cranial nerve palsies, loss of deep tendon reflexes, and a spinal fluid protein of 2,040 mg. per cent. In a few weeks the clinical picture changed completely. Choked discs developed; the paralysis became spastic in type; the deep tendon reflexes were hyperactive and the Babinski sign was positive bilaterally. The child had a glioma of the brain stem and expired before an operation could be done.

Toxic and metabolic disorders of the central nervous system were found in thirteen patients admitted with the tentative diagnosis of poliomyelitis. Two cases of *tetanus,* with hyperirritability, headache, muscle pain, and spasm as presenting symptoms, were seen. In the early stages, the patient with tetanus exhibits intermittent tonic spasms of muscles. Trismus is a prominent feature. This does not occur in poliomyelitis. As the disease progresses the spasm becomes continuous. A history of trauma, normal spinal fluid, and the presence of intermittent muscle spasm rule out poliomyelitis.

Lead poisoning was diagnosed in two cases. Irritability, headache, papilledema, vomiting, convulsions, and peripheral motor paralysis were the symptoms which prompted the provisional diagnosis of poliomyelitis. The slow onset, anemia with basophilic stippling, and the increased density

at the ends of the long bones as seen on the roentgenogram substantiated the diagnosis of lead intoxication. The cerebrospinal fluid is normal in this disease.

One case of *acute porphyria* was seen. Neurological symptoms may be prominent. Severe muscle pains, lower motor neuron weakness in the extremities, bulbar palsies, and loss of deep tendon reflexes present a problem in diagnosis. Mental symptoms may be outstanding.[15]

Our patient was a 29-year-old white female who was disoriented and had hallucinations. She complained of muscle pains and weaknesses. The urine was characteristically red-brown in color and contained an abnormal quantity of porphyrins. After discharge from the hospital the patient had several remissions and exacerbations. She expired suddenly as a result of respiratory paralysis about one year after the onset of the disease. The spinal fluid examination was within normal limits. This is the usual finding, although Lyons[16] reports a case with elevated protein and cells.

One case of *tick paralysis* was admitted as poliomyelitis and has been reported elsewhere.[17] Predominant features of the disease are progressive, ascending paralysis, decreased to absent deep tendon reflexes, loss of position sense in varying degrees, and normal spinal fluid findings. There is no evidence of meningeal irritation. The dramatic relief of symptoms upon the removal of the dog tick, *Dermacentor variabilis Say*, or the wood tick, *Dermacentor andersoni Stiles*, establishes the diagnosis.

Vascular lesions of the central nervous system were present in twelve patients admitted to the poliomyelitis ward. Paralysis, in these patients, was flaccid at the onset, and deep tendon reflexes frequently could not be elicited. As the disease progressed, spasticity of muscles and hyperactive reflexes appeared. The Babinski sign was positive on admission or soon thereafter. The sudden development of unconsciousness followed by hemiplegia and, usually, cranial nerve weakness, rules out poliomyelitis.

Cerebral hemorrhage due to hypertensive cardiovascular disease, *thrombosis* due to arteriosclerotic vascular disease, and *cerebral embolism* secondary to bacterial endocarditis comprised seven of the twelve vascular lesions. Two patients had signs of meningeal irritation which frequently occurs in rupture of a congenital aneurysm. The history of abrupt onset with headache followed by nuchal rigidity, usually without muscle weaknesses, should suggest the diagnosis of a ruptured aneurysm. The spinal fluid may be bloody, if the hemorrhage is into the subarachnoid space.

Encephalopathy was seen in a 12-year-old Negro male with sickle-cell anemia. He had had six crises previously, with back and leg pain. On admission to the Philadelphia Hospital for Contagious Diseases he complained of a stiff neck and back pain. The Kernig sign was positive and the deep tendon reflexes were absent. There was no motor or sensory impairment. There was marked sickling of the peripheral red blood cells and the cerebrospinal fluid was within normal limits. Therapy consisted of several whole blood transfusions. He recovered in twelve days and remained well until eighteen months later when there was a recurrence of the above clinical picture. Since then there were numer-

ous hospitalizations for the treatment of anemia. Gordon and Gardner reported a case of sickle-cell encephalopathy in a white male thought to be poliomyelitis because of back and leg pain, inability to void, and the loss of deep tendon reflexes.[18] These symptoms are not uncommon with central nervous system involvement of the disease. Vessels of the cortex and meninges are occluded by sickle red cells and the resultant clinical syndrome may be confused with poliomyelitis. Except for increased pressure the cerebrospinal fluid is normal.

TABLE II. PERIPHERAL NERVE DISEASES

CLASSIFICATION		NUMBER OF CASES
I. Trauma Neuritis		4
(a) Erb's palsy	2	
(b) Peroneal palsy	1	
(c) Sciatic nerve palsy	1	
II. Postinfectious Neuritis		2
(a) Peroneal neuritis	1	
(b) Brachial plexus neuritis	1	
III. Nutritional Neuritis		2
(a) Alcoholic polyneuritis	2	
Grand Total		8 cases

2. *Peripheral Nerve Diseases* (Table II).—Peripheral nerve diseases constituted eight of the total number of cases in the study. Involvement of a peripheral nerve, whether following injury or infection, results in paresis without signs of meningeal irritation. Pain along the distribution of the nerve may be a prominent symptom. Tendon reflexes are decreased or absent and some sensory changes occur in most cases. The diagnosis of *alcoholic polyneuritis* seldom presents difficulties. This diagnosis is based on the history of alcoholism, severe pain in muscle groups or along nerve trunks, weakness of extremities with foot drop or wrist drop, and sensory changes. The spinal fluid is normal.

In small infants paralytic poliomyelitis may occur without meningeal signs. The disease may be confused with peripheral neuritis unless a lumbar puncture is done. The spinal fluid is normal in peripheral neuritis.

TABLE III. PSYCHOGENIC DISORDERS

CLASSIFICATION	NUMBER OF CASES
I. Hysteria (conversion type)	12
II. Cephalalgia (psychogenic etiology)	1
Grand Total	13 cases

3. *Psychogenic Disorders* (Table III).—Thirteen of our patients were found to have a psychosomatic basis for the symptoms leading to a tentative diagnosis of poliomyelitis. Twelve cases, all female, presented paralysis associated with anxiety and hyperesthesia. Some of the patients had bizarre sensory disturbances. One patient developed bilateral carpal-pedal spasm after being told that she might have poliomyelitis. The differentiation between *hysteria* and poliomyelitis is not always simple. Weakness of muscle groups may be a persistent complaint; however, the physical findings are not always consistent. Reflexes are normal to hyperactive. That the sensory impairment is not organic often can be suspected by the bizarre distribution of these changes. Signs of meningeal irritation are usually absent or may be equivocal if the patient's cooperation is poor. The spinal fluid is normal. A careful history will bring to light a definite emotional background to the illness. Most of our patients improved immediately when they learned the reason for their symp-

toms, but psychiatric treatment may be necessary in some patients.

4. *Respiratory Infections* (Table IV).—Complaints referable to the respiratory system are common in the early stages of poliomyelitis. Consequently, in the poliomyelitis season, it is wise to observe any patient with respiratory system symptoms for one week, until the danger of possible central nervous involvement is past. Children exhibiting *cervical adenitis* frequently react as if they have nuchal rigidity. Thirty of our cases had bacterial infections of the nose and throat.

TABLE IV. RESPIRATORY INFECTIONS

CLASSIFICATION		NUMBER OF CASES
I. Upper respiratory infection—common cold thought to be viral in origin		59
II. Acute tonsillitis, pharyngitis, rhinitis, bacterial infections		30
III. Pneumonia		13
(a) Lobar pneumonia, 4 cases with meningismus	8	
(b) Bronchopneumonia	5	
IV. Acute otitis media, 1 case with meningismus		4
V. Acute tracheobronchitis		4
VI. Acute sinusitis with toxic labyrinthitis		1
VII. Retropharyngeal abscess		1
VIII. Acute obstructive laryngitis		1
IX. Acute bronchial asthma		1
Grand Total		114 cases

Many of them complained of neck pain which was caused by tender, enlarged cervical lymph nodes. Thirteen patients with *pneumonia* were admitted with the diagnosis of poliomyelitis. Four of the eight patients with *lobar pneumonia* had *meningismus*. The differential diagnosis between respiratory infections and poliomyelitis is not difficult but requires a careful examination of the ears, nose, throat, and chest. Actual inflammation of the mucous membranes is not common in poliomyelitis even when sore throat is the chief complaint. For this reason, sore throat in poliomyelitis is considered by some authors to be neuritic in origin.[19] A spinal fluid examination should be done if meningeal irritation is present or is suspected.

Bulbar poliomyelitis was thought to be present in seven of our patients because of the finding of respiratory difficulty. These diseases include *retropharyngeal abscess, obstructive laryngitis, acute tracheobronchitis,* and *bronchial asthma.* A careful history and physical examination should make these diagnoses obvious.

An *upper respiratory infection* or "common cold" was the only finding in fifty-nine cases. These patients may have had abortive poliomyelitis but without a diagnostic laboratory test or evidence of central nervous system disease, it was not possible to make an unequivocal diagnosis of poliomyelitis.

5. *Musculoskeletal Diseases* (Table V).—Seventy-seven patients were admitted with diseases of the musculoskeletal system. Muscle spasm as a result of trauma to bone, muscle, joint disease frequently caused symptoms suggesting poliomyelitis. Joint pain is often responsible for the unwillingness of the patient to move an extremity. The disinclination or refusal to stand or walk because of local pain, especially in children, was frequently interpreted as evidence of muscle weakness. Twenty-seven patients with *acute rheumatic fever* were admitted as poliomyelitis in the period covered by this survey. All of the patients had arthritis as the most prominent symptom. Spinal fluid and physical examination failed to reveal any disease of the central nervous system. Occasion-

ally, when the hip was involved, muscle spasm about the joint resembled the hamstring tightness usually seen in poliomyelitis. A positive Patrick sign aided in localizing the disease to the hip. Serial erythrocyte sedimentation rates and electrocardiograms were valuable in substantiating the diagnosis of rheumatic fever.

ties the patient was thought to have poliomyelitis. The roentgenogram findings of typical periostitis, a positive blood Wassermann, and normal cerebrospinal fluid established the diagnosis.

Scurvy was present in one infant who had irritability, pseudoparalysis, frog-leg attitude, and pain on motion

TABLE V. MUSCULOSKELETAL DISEASES

DISEASES				NUMBER OF CASES
I. Bone and Joint Diseases				57
(a) Infections			42	
1. Arthritis		33		
Acute rheumatic fever with joint involvement	27			
Acute arthritis—cause not determined	3			
Rheumatoid arthritis	2			
Toxic arthritis	1			
2. Osteoarthritis		3		
Staphylococcal osteoarthritis	2			
Tuberculous osteoarthritis	1			
3. Osteomyelitis		3		
4. Acute epiphysitis		2		
5. Osteitis and periostitis (syphilitic)		1		
(b) Arthralgia (cause undetermined)			7	
(c) Trauma			5	
Trauma of hip or back		3		
Slipped right femoral epiphysis		1		
Fractured left femur		1		
(d) Congenital defects			2	
Spina bifida occulta		1		
Congenital deformity lumbar spine (with low back pain)		1		
(e) Metabolic disorders (scurvy)			1	
II. Muscle Involvement				20
(a) Trauma		9		
(b) Myositis		9		
Nonsuppurative myositis (myositis of neck in 4 pts.)	7			
Suppurative myotenosynovitis	1			
Parasitic infestation (trichinosis)	1			
(c) Metabolic and degenerative diseases		2		
Pseudohypertrophic muscular dystrophy	1			
Periodic familial paralysis	1			
			Grand Total	77 cases

Osteomyelitis, osteoarthritis, acute epiphysitis, or ***periostitis*** was seen in nine patients. Localized pain, fever, and toxicity were common symptoms. Roentgenograms in the early stages do not show evidence of disease. Severe pain in the arms and legs was noted in one case of congenital syphilis. Because of the paralysis of the extremities the patient was thought to have poliomyelitis. The roentgenogram findings of typical periostitis, a positive blood Wassermann, and normal cerebrospinal fluid established the diagnosis.

Scurvy was present in one infant who had irritability, pseudoparalysis, frog-leg attitude, and pain on motion of the legs. Roentgenograms showed the typical lesions of scurvy.

Trichinosis was found in one patient. Muscle pain, muscle spasm, fever, and malaise were the chief complaints. Eosinophilia, a history of raw pork ingestion, and encysted trichina in muscle, as demonstrated by muscle biopsy, led to the diagnosis.

One case of *pseudohypertrophic muscular dystrophy* was seen. The muscle weakness and atrophy in this disease are slowly progressive; fever and symptoms referable to the central nervous system are absent. The disease is usually hereditofamilial.

Periodic familial paralysis accounted for the admission of one patient as poliomyelitis. This patient, a 12-year-old male, awoke one day with quadriplegia. Examination revealed a flaccid quadriplegia, absent tendon reflexes, and a normal temperature. There were no signs of meningeal irritation and the spinal fluid was normal. He recovered completely within four days. These findings, and a history of similar episodes in another member of his family, suggested the diagnosis of periodic familial paralysis.

TABLE VI. GASTROINTESTINAL DISEASES

DISEASES		NUMBER OF CASES
I. Gastroenteritis (vomiting and abdominal pain). 2 cases with meningismus		10
II. Diarrhea		7
(a) Etiology unknown	5	
(b) Typhoid fever	1	
(c) Shigella dysentery	1	
Grand Total		17 cases

6. *Gastrointestinal Diseases* (Table VI).—Gastrointestinal symptoms may be present in the prodromal stages of poliomyelitis. However, we have not found either diarrhea or constipation to be too frequent a complaint in our poliomyelitis patients.

Seventeen patients with negative physical findings and normal cerebrospinal fluid were thought to have poliomyelitis because of diarrhea or vomiting. Two children in the group were brothers of a patient who was in the hospital with poliomyelitis. They had normal spinal fluid and no abnormal neurological finding. It is probable that they had the abortive form of the disease.

7. *Genitourinary Diseases* (Table VII).—Diseases of the genitourinary system were found in eighteen patients admitted to the poliomyelitis ward. The most common complaint was back pain. Infants with *acute infections of the urinary tract* frequently were noted to have only fever and irritability. It was not difficult to differentiate these diseases from poliomyelitis. The back pain invariably was found to be in the costovertebral angle. A suggestive urinalysis in the absence of disease of the central nervous system led to the correct diagnosis.

TABLE VII. GENITOURINARY DISEASES

DISEASES		NUMBER OF CASES
I. Infections		11
(a) Pyelonephritis	8	
(b) Cystitis	1	
(c) Perinephric abscess	1	
(d) Rectovaginal fistula (with infection)	1	
II. Toxic Disorders		3
(a) Acute glomerulonephritis	2	
(b) Chronic glomerulonephritis	1	
III. Functional Disorders		3
(a) Dysmenorrhea	2	
(b) Menorrhagia	1	
IV. Tumors		1
(a) Wilms' tumor	1	
Grand Total		18 cases

One 3-year-old child had a *Wilms' tumor*. His complaints of fever, back pain, and irritability were due to a tumor mass in the left upper quadrant of the abdomen.

8. *Diseases of the Skin and Allied Structures* (Table VIII).—Frequently, small children and infants are admitted during poliomyelitis season with only a slight fever and irritability. Four patients with these com-

TABLE VIII. DISEASES OF THE SKIN AND ALLIED STRUCTURES

DISEASES		NUMBER OF CASES
I. Rashes (with fever and irritability)		4
(a) Miliaria	2	
(b) Allergic dermatitis	1	
(c) Exanthema subitum	1	
II. Infections		6
(a) Infected insect bites	2	
(b) Impetigo contagiosum (with pseudoparalysis)	1	
(c) Furunculosis of left popliteal area	1	
(d) Cellulitis of left knee	1	
(e) Cellulitis of back	1	
Grand Total		10 cases

plaints were diagnosed variously as having *miliaria, allergic dermatitis,* and *exanthema subitum.*

Infections of the subcutaneous tissues of the extremities produced pain and pseudoparalysis in five small children. One patient had nuchal rigidity and spasm of the muscles of the back which suggested meningeal irritation. His symptoms resulted from an extensive cellulitis of the right side of the back.

TABLE IX. ACUTE FEBRILE ILLNESSES

DISEASES	NUMBER OF CASES
I. Malaria	2
II. Infectious hepatitis	1
III. Fever of unknown origin	1
IV. Infectious mononucleosis (joint pain and meningismus)	1
Grand Total	5 cases

9. *Acute Febrile Illnesses* (Table IX).—Five cases could not be classified under any of the foregoing groups. The symptoms in these patients were generalized and involved a number of systems of the body. The diseases include *malaria, infectious hepatitis, fever of unknown origin,* and *infectious mononucleosis.* None of the patients presented findings suggesting central nervous system involvement as expected in poliomyelitis. However, an acute febrile episode during the poliomyelitis season is sufficient reason for entertaining the diagnosis.

COMMENT

There is a relatively high incidence of revised diagnoses in patients who were suspected of having poliomyelitis. Our rate of revised diagnoses was 28.9 per cent which compares favorably with what was reported by others[20, 21] but is much lower than the 49.8 per cent reported by Gordon.[22] Twenty-eight per cent of the revised diagnoses had a disease of the central nervous system, other than poliomyelitis, indicating that the suspicion of poliomyelitis was amply justified. It is gratifying to see that 28 per cent of the revised diagnoses had acute respiratory infections, reflecting a high degree of suspicion by the referring physicians during the poliomyelitis season. There was a surprisingly large number of patients (twenty-seven) with acute rheumatic fever, a fairly common disease of childhood.

The facility with which an accurate diagnosis of poliomyelitis is made varies with the stage of the disease. At best, the diagnosis is made by exclusion but in the advanced stages when there is central nervous system involvement and flaccid paralysis the diagnosis of poliomyelitis may be readily presumed. Difficulties in differential diagnosis are frequently the result of hasty, inadequate examination and the improper evaluation of the signs and symptoms. All studies available should be employed to determine the cause of the patient's complaints. In the absence of disease of the central nervous system, spinal fluid pleocyto-

sis, and lower motor neuron paralysis, poliomyelitis is unlikely. The spinal fluid should be examined in every patient who demonstrates acute disease of the central nervous system. Routine blood virus studies should be performed in every patient with a spinal fluid pleocytosis who does not have flaccid paralysis.

SUMMARY

In the ten years from 1940 through 1949, 1,420 cases were admitted to the Philadelphia Hospital for Contagious Diseases with the diagnosis of acute anterior poliomyelitis. In 409 of these patients (28.9 per cent) this diagnosis was not substantiated. A follow-up study of the patients who did not have poliomyelitis was conducted.

Seventeen of the 409 cases were undiagnosed, but three of these patients were later diagnosed as poliomyelitis by other physicians. Posthospitalization histories did not reveal any illness in the other fourteen patients. No disease was found in seventeen other patients. These children also remained well after discharge.

A classification of the diseases according to the poliomyelitis-like symptoms is presented. The differential diagnosis is discussed briefly.

We wish to acknowledge the assistance of Seymour Ledis, M.D., in the study.

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AUREOMYCIN IN THE TREATMENT OF BETA HEMOLYTIC STREPTOCOCCAL INFECTIONS

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ALTHOUGH aureomycin has been found to be effective in vitro against beta hemolytic streptococcal infections[1, 2] its value in illness caused by this organism has received slight attention. This communication reports the results obtained with aureomycin in the home treatment of the beta hemolytic streptococcal infections seen in pediatric practice.

MATERIAL AND METHODS

During the period from November, 1949, through June, 1950, fifty children were treated at home for bacteriologically proved beta hemolytic streptococcal infections with varying dosage schedules of aureomycin. In the series were twenty boys and thirty girls distributed in age as follows:

Under 2 years	1
2 through 5 years	12
6 through 10 years	31
11 through 15 years	6
	50

Sixty-four separate streptococcal infections occurred in this group during the period observed. There were fifty-one attacks of streptococcal sore throat without rash, three attacks with rash (scarlet fever), two of cervical adenitis, three of otitis media, one of vaginitis, and four asymptomatic carriers. Fifty-eight of these infections were treated with aureomycin.

These children were seen initially either in their homes or in my office. Throat swabs were obtained. These swabs were placed in rubber-stoppered tubes containing sufficient Douglas broth to keep them moist until they could be transferred to blood agar plates. These plates were incubated overnight and sent to the Rheumatic Fever Laboratory for bacteriologic diagnosis and isolation of any beta hemolytic streptococci. Seventeen of the isolated strains were grouped and typed by the capillary tube precipitin method of Swift, Wilson, and Lancefield.[3] These strains were tested against sera—1, 6, 12, 13, 14, 15, 17, 18, 19, 22, 23, 24, 28, 29, 30, 31, 33, 36, 38, 39, 40, 42, 46, 47. Two sera, 3 and 5, which had previously been found commonly in this area, were not available.

Repeated cultures were taken (total 212). The throats of six patients were cultured twice, sixteen three times, ten four times, and eighteen five or more times. Patients were observed for varying periods of time. If a patient's illness recurred and he was treated by some other method, the follow-up period was considered terminated at the time the new treatment was begun. A generally successful attempt was made to see all patients at least until cultures were negative, and until they were asymp-

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tomatic and had normal sedimentation rates. They were warned, however, to report any symptoms which occurred after discharge from observation. Since they were private patients, subsequent illnesses would have been reported to us. The length of observation for the immediate illness after completion of treatment was:

None	3
1-7 days	10
8-14 days	6
15-21 days	6
22-28 days	5
More than 28 days	20
	50

In addition to clinical examination and culture for bacteria, repeated blood samples were obtained from the majority of children for sedimentation rates, assay of antistreptolysin and antihyaluronidase.

Sedimentation Rates.—The micromethod of Landau[4] was used. One or more tests were done during or after forty-eight infections. In general, patients whose tests became normal early were not observed as long as those whose tests seemed to be persistently abnormal. (By this method a fall of 15 mm. per hour is considered the upper limit of normal.)

Antistreptolysin "O" Titer.—The method of Rantz and Randall[5] for titrating antistreptolysin was used. For producing and standardizing streptolysin Massell's revision of the methods of Todd[6] and of Hodge and Swift[7] was utilized. An increase of titer of two or more tubes was considered significant. Thirty-one patients had at least two determinations of ASO titer. In all but three of these patients the initial blood was obtained within a week of onset. The second blood sample was obtained at least ten days after the first in all but one patient, and in nineteen, at least three weeks after the initial sample.

Antihyaluronidase Titer.—The mucin clot method was used. We followed the procedure of Jablon[8] slightly modified by Jaecox.[9] By this method, a rise of at least 40 units was considered significant. Seventy-nine titers were obtained on twenty-seven patients all of whom had more than one determination. In these twenty-seven patients the original blood was obtained within one week of onset in twenty-two, in one each on the eighth, ninth, and fourteenth days, and in two the time of onset was unknown. The last blood sample was obtained in one, one week after onset; in one, between one and two weeks; in four between two and three weeks; in three between three and four weeks; and in eighteen, four weeks or longer after onset.

Aureomycin Dosage.—The initial dose given was 5 mg. per kilogram of body weight in twenty-four hours and calculated to the nearest 50 mg. In ten patients the initial dose was used for four days (in one case five days); in the remaining cases for two days. The dose was then reduced to half this level and continued for a total period of from four to twelve days. Medication was given orally during the waking periods in capsules or mixed with chocolate powder.

RESULTS

Clinical and Bacteriologic.—The immediate clinical response in all cases was gratifying. Fever and other symptoms as well as clinical signs usually disappeared within twenty-four hours, and, with the exception of

TABLE I. RELATION OF DURATION OF TREATMENT TO RECURRENCE

DURATION TREATMENT DAYS	NUMBER ILLNESSES	ILL AND POSITIVE CULTURE	NOT ILL POSITIVE CULTURE
12	12	4	0
10	29	5	3
9	3	0	1
8	5	0	2
7	3	0	0
6 or under	4	3	1
Unknown*	2	0	0
	58	12	7

*Probably ten days.

suppurative lesions such as otitis media which took somewhat longer, always within forty-eight hours. The symptoms and signs remained normal in all cases and no complications occurred during the period of therapy. All cultures taken forty-eight hours or more after beginning treatment and while aureomycin was being given were negative for beta hemolytic streptococci (sixty-three negative cultures, 0 positive).

However, in fifty-eight attacks of streptococcal disease treated with aureomycin there were twelve clinical recurrences of the disease with positive cultures and seven recurrences of positive cultures without clinical symptoms after treatment was stopped. The relation of these to duration of treatment is given in Table I and the details of the individual cases in Table II.

Aside from the recurrences listed one mild attack of otitis media, one mild attack of cervical adenitis, and one episode of fever lasting one day, all with negative cultures for hemolytic streptococci, occurred in the group. No late complications such as nephritis or rheumatic fever were observed.

Group and Type of Streptococci Found.—Of the seventeen strains tested all were Group A. Of these,

TABLE II. RECURRENCES OF STREPTOCOCCAL INFECTION TREATED WITH AUREOMYCIN

CASE	AGE	SEX	ORIGINAL DIAGNOSIS*	DURATION TREATMENT DAYS	TYPE RECURRENCE*	CULTURE	DAY OF RECURRENCE AFTER TREATMENT	REMARKS
A. A.	6	F	S.T.	10	S.T.	4 plus	14	Milder than first
J. C.	9	F	S.T.	5	S.T.	4 plus	3	Milder than first
D. D.	5	F	S.T.	12	S.T.	4 plus	4	All in same family
E. D.	2	F	S.T.	12	S.T.	2 plus	4	Mother also had sore throat
P. D.	9	F	S.T.	12	S.T.	4 plus	4	
J. F.	5	F	O.M.	10	O.M.	3 plus	3	
A. G.	11	M	C.	6	C.	4 plus	29	Same family
W. G.	15	M	S.T.	10	S.T.	4 plus	38	Both A 1
R. G.	5	M	S.T.	10	C.	3 plus	42	
W. H.	2	M	O.M.	8	C.	4 plus	1	Mild
C. H.	4	F	S.T.	6	S.T.	4 plus	1	Milder than first
B. J.	6	F	S.F.	10	S.T.	4 plus	2	
B. L.	6	F	S.T.	12	S.T.	4 plus	4	
D. R.	6	M	S.T.	8	C.	1 plus	16	Mildly ill
J. W.	9	F	S.T.	4	S.T.	4 plus	4	
J. W.	9	F	S.T.	10	C.	4 plus	31	Cult. neg. 20 days later S R
L. W.	6	F	S.F.	10	S.T.	4 plus	6	
L. W.	6	F	S.T.	10	C.	2 plus?	1	Plate broken before isolation, may have been negative
S. Z.	5	F	S.T. O.M.	9	C.	1 plus	15	

*S.T. = Strep. throat. S.F. = Scarlet fever. O.M. = Otitis media. C. = Carrier.

eight were type 1, three type 6, and in six no type could be determined. From previous local experience it is probable that some of the six nontypable strains might have been found to be type 3 or 5 had these sera been available for testing. In one child type 6 was isolated first, and in a subsequent attack three months later, type 1. In a second child type 1 was isolated twice, with one negative culture between the two isolations. His recurrence occurred after six days of aureomycin treatment. In both cases second treatment with aureomycin was effective. The response to treatment did not seem to bear any relation to type.

Sedimentation Rate.—As indicated in Table III the majority of patients tested had elevated sedimentation (59 per cent) rates in the first week after beginning treatment, although a number of these tests were taken after the patient was afebrile and symptomatic. Even in the fourth week and beyond, six out of twenty-six patients tested had high rates. In one of these cases otitis media and a recurrent streptococcal sore throat developed two days later, in two others a nonstreptococcal respiratory infection was present. However, in the remaining three no infection was found.

It would seem therefore that aureomycin was not uniformly successful in bringing the sedimentation rate to normal early after streptococcal infections. The relatively high proportion of elevated rates in the second week and beyond was probably more apparent than real since those with normal tests were frequently not followed as long as those with abnormal values. However, the presence of a normal sedimentation rate did not necessarily rule out further trouble, since in two cases recurrences of streptococcal infections followed in patients who had had normal sedimentation rates.

TABLE III. SEDIMENTATION RATES AFTER AUREOMYCIN TREATMENT

	NUMBER PATIENTS TESTED	NUMBER RATE OVER 15	% RATE OVER 15
In 1st week	27	16	59
In 2nd week	13	4	31
In 3rd week	15	4	27
Beyond 3rd week	26	6	23

Antistreptolysin Titer.—The antistreptolysin titer showed no rise in fifteen patients, three patients showed a rise in their titer of one tube, five of two tubes, and in eight a rise of three or more tubes. Thus thirteen or 42 per cent of the patients treated with aureomycin showed significant antibody response as measured by antistreptolysin "O."

Antihyaluronidase Titer.—In one patient the antihyaluronidase titer rose to 60 units; in three to 40 units, in two to 20 units, and in one to 10 units. In the remaining twenty no rise was observed. Since a significant rise should be at least to 40 units, only four or 15 per cent showed significant antibody response as measured by antihyaluronidase titer.

Drug Toxicity.—No toxic reactions of consequence were seen. On the small dose given occasional nausea and vomiting occurred but were minimal. Loose stools and anorexia during treatment were common, but never of major importance. A few patients were not included in the series because the parents were unable to give the medication to their refractory children.

DISCUSSION

Finland and co-workers[1, 10] in vitro studies have demonstrated that aureomycin is effective in inhibiting the growth of beta hemolytic streptococci at levels which can be obtained in man (0.4 to 16.0 μg per milliliter) and that the Lancefield type bears little relation to sensitivity and that resistance to this antibiotic seldom develops.

However, their in vitro studies[1] have also shown that penicillin is some eighty times more effective than aureomycin in inhibiting growth of beta hemolytic streptococci. This fact plus the excellent clinical response of beta hemolytic streptococcal infections to penicillin have made this antibiotic the drug of choice in treating this group of diseases. Consequently reports on the clinical use of aureomycin in treatment of streptococcal infections have been limited. Satisfactory responses, however, have been reported in cases of tonsillitis,[11] erysipelas,[12] sinusitis,[13] peritonitis,[14, 15] and streptococcal pneumonia.[16] Studies from the Streptococcal Disease Laboratory of the Army Air Force at Fort Warren, Wyoming,[17] showed that aureomycin seemed slightly more effective in reducing the symptoms of streptococcal disease than penicillin but were ineffectual in eliminating the streptococci from the throat. However, even though penicillin is the drug of choice, a sufficient number of patients are sensitive to penicillin to make it advisable to assay the value of other antibiotics.

Our studies indicated that with relatively small doses of aureomycin streptococcal infections were rapidly improved clinically, and that hemolytic streptococci, within a short period of time, were no longer cultured from the throat. However, when the aureomycin was discontinued in some patients, both bacteriologic and clinical recurrence (or reinfection) occurred, usually within a week of discontinuing medication. In general, such clinical recurrences were milder than the original attack and occurred in about 20 per cent of cases. Known bacteriologic recurrences without symptoms were noted in approximately 10 per cent—an over-all recurrence rate of about 30 per cent. More complete studies would probably show even higher rates. In all cases where aureomycin was used a second time clinical response was as good as in the primary attack. A treatment period of at least a week seems essential, but does not guarantee prevention of reinfection or recurrence.

Significant antibody response as measured by antistreptolysin titer and antihyaluronidase titer occurred in 42 per cent and 15 per cent, respectively, of patients treated with aureomycin. As compared with these antibody responses found by others after streptococcal infections,[18, 19] the proportion of patients who developed increased antibody titer in our series is low. However, they occurred with sufficient frequency to prove that aureomycin would not prevent such response in some patients.

Although persistently elevated sedimentation rates were not the rule after the use of aureomycin, they did occur in about 25 per cent of patients.

Pyogenic complications were uncommon, and no known cases of either rheumatic fever or nephritis occurred.

Toxicity was minimal from aureomycin and no evidence of sensitivity was encountered. Whether larger

doses of aureomycin would be more effective in preventing recurrences or would prove to be bactericidal to the streptococcus could not be determined from this study.

SUMMARY

Aureomycin in relatively small doses was an effective medication against beta hemolytic streptococcal infections. Its immediate clinical effect was excellent, but bacteriologic and clinical recurrences appeared in a moderate number of cases, even when the patients were treated for as long as twelve days. Antibody response as measured by antistreptolysin and antihyaluronidase titer appeared in a minority of patients treated by this antibiotic. In a few patients persistently high sedimentation rates followed its use. Early pyogenic complications were uncommon and late complicaions such as rheumatic fever or nephritis were not observed.

Dr. Ralph Jaecox's laboratory measured some of the antihyaluronidase titers.

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STABILITY OF ASCORBIC ACID IN MILK AT DIFFERENT STAGES OF PROCESSING

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MILK from various species of animals has been continuously included in the human diet since early antiquity. Apparently, empirical observations convinced early man that milk was a satisfactory food. With the passage of time, more and more information has been collected regarding the composition and nutritive value of milk until it is now generally agreed that milk is one of the most complete foods included in the present human dietary. Unfortunately, milk, which is a satisfactory source of so many dietary essentials, contains an inadequate amount of reduced ascorbic acid (vitamin C) when it reaches the ultimate consumer. Studies of the composition of freshly drawn milk have repeatedly indicated that milk as it leaves the cow contains a considerable amount of ascorbic acid. In fact, Sharp, Guthrie, and Hand[1] reported that the milk produced annually in this country, as it is drawn from the cows, contains as much ascorbic acid as is present in the entire citrus crop of the United States. However, the larger portion of the ascorbic acid originally present in milk never reaches the ultimate consumer. It is lost during the processing, distribution, and storage of milk. For instance, Sharp, Guthrie, and Hand[1] found 22.2 mg. of ascorbic acid per liter in freshly drawn milk and an average of 2.9 mg. per liter in 1,502 samples of commercial, bottled, pasteurized milk collected from various areas in New York State, indicating that nearly 90 per cent of the ascorbic acid was lost before the milk was ingested by the ultimate consumer. Numerous investigations have been conducted to accumulate information regarding the conditions that cause this enormous loss of a vitamin essential for normal human nutrition. A recent study[2] in this laboratory has shown that samples of milk taken at different stages of processing contained widely different amounts of ascorbic acid. The study reported here was undertaken to determine the stability of ascorbic acid in milk at different stages of processing.

Contribution No. 817, Massachusetts Agricultural Experiment Station.

EXPERIMENTAL

The milk used in this study was mixed herd milk produced by the University purebred Ayrshire, Guernsey, Holstein, Jersey, and Shorthorn cows. It was a mixture of evening and morning milk pasteurized in the morning by the holding method at 143° F. for thirty minutes. The equipment was similar in construction and capacity to that used by commercial dairies. The milk was pasteurized in a covered, 850-quart stainless steel vat equipped with stainless steel paddles for agitating the milk. Shortly after pasteurization was started the small head space above the milk became filled with vapor from the heating of the milk, and atmospheric oxygen was eliminated from the pas-

teurizer. When pasteurization was completed, the milk was passed through nickel alloy metal pipes to a brass pump and over a covered tinned-copper surface cooler to the bottle filler, which held the milk in a stainless steel bowl. At the middle of the experimental period the brass pump was replaced with a stainless steel pump.

Milk was collected at approximately two-week intervals throughout the school year. At each of the twenty-two test periods four samples were collected: one sample from the pasteurizing vat represented the thoroughly mixed cold milk before pasteurization was started; a second sample came from the vat as soon as pasteurization had been completed; the third sample was taken from the first milk that came through the bottling equipment; and the fourth sample was from the last milk to pass through the cooling and bottling equipment. All samples were cooled at once at 40° F., then taken to the laboratory and assayed immediately for ascorbic acid. To test the stability of the ascorbic acid the samples were subsequently assayed at four twenty-four-hour periods. During the ninety-six-hour observation period the samples were stored in darkness at 10° C. in an electric household-type refrigerator. The ascorbic acid assays were made by the Sharp[3] rapid method as modified by Holmes.[4]

RESULTS AND DISCUSSION

The results of the 412 assays of milk collected at the different stages of processing are summarized graphically in Fig. 1. The average amount of ascorbic acid in the various lots of the mixed cooled herd milk before pasteurization was 18.4 mg. per liter. After pasteurization but before the milk was removed from the vat, the ascorbic acid of the several lots of milk averaged 17.3 mg. As a consequence of the air within and the metallic composition of the pipe line and cooling and bottling equipment, the first milk to come through the equipment contained, as an average, only 6.4 mg. of ascorbic acid per liter; but after the equipment had been thoroughly flushed out, the last milk through the equipment contained 15.4 mg. per liter. These average values obtained for the samples of milk taken at the four stages of processing are represented as the initial points of the four curves in Fig. 1. After ninety-six hours of storage the average values for milk sampled at the four stages of processing were 6.9, 6.8, 3.0, and 4.1 mg., respectively, of ascorbic acid per liter; these values represent the final points on the curves in Fig. 1.

The first milk through the equipment lost 49 per cent of its ascorbic acid during the first forty-eight hours in the refrigerator and 4 per cent during the second forty-eight hours, or a total of 53 per cent. The last milk through the equipment lost 58 per cent of its ascorbic acid during the first forty-eight hours storage and 15 per cent during the next forty-eight hours, or a total of 73 per cent. However, the last milk still retained 4.1 mg. of ascorbic acid per liter as compared with 3.0 mg. retained by the first milk. Even though the loss of ascorbic acid during the first two days storage was much more rapid from the last milk through the equipment than from the first milk, the last milk contained nearly twice as much ascorbic acid, i.e., 6.5 and 3.5 mg. per liter, respectively.

The raw milk with 18.4 mg. of ascorbic acid per liter lost 63 per cent during storage, and the freshly pasteurized milk taken directly from the stainless steel vat lost 61 per cent of its ascorbic acid during ninety-six hours in the refrigerator. Thus, the stability of the ascorbic acid in the raw and in the freshly pasteurized milk that had not passed through the cooling and bottling equipment was essentially the same. Considered from a practical standpoint, the 63 per cent loss found in this study is identical with the 64 per cent average loss of ascorbic acid from raw milk reported in an earlier study.[5] The 77 per cent loss of ascorbic acid during ninety-six hours storage of pasteurized milk noted in the previous study is definitely greater than the 61 per cent reported here for pasteurized milk taken from the pasteurizing vat but is in close agreement with the 73 per cent loss observed in this study for the last pasteurized milk passed through the equipment. This was to be expected since the conditions and equipment were essentially the same in both instances.

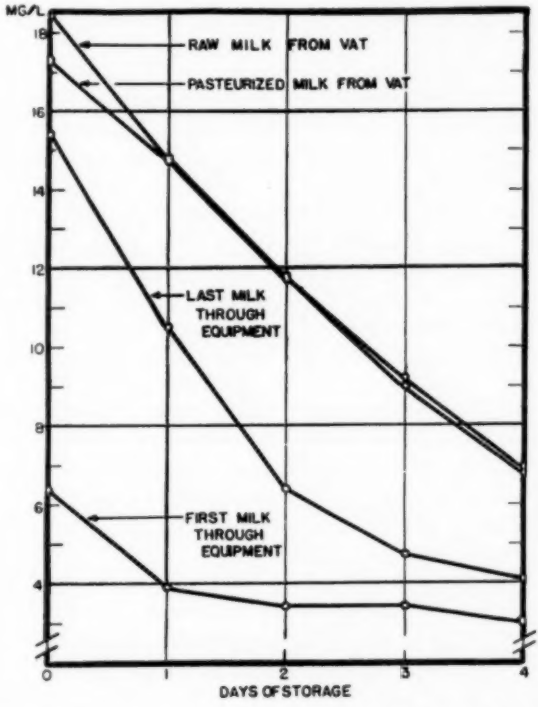

Fig. 1.—Loss of reduced ascorbic acid as affected by different stages of processing.

The 6 per cent pasteurization loss of ascorbic acid, 18.4 to 17.3 mg., for the treated milk that was taken directly from the stainless steel vat is decidedly less than that reported by Holmes, Tripp, Woelffer, and Satterfield,[6]

Woessner, Weckel, and Schuette,[7] Elvehjem,[8] Holmes, Jones, Wertz, and Kuzmeski,[9] Mawson and Kon,[10] and others, but the loss of 16 per cent of ascorbic acid for the last milk through the cooling and bottling equipment is of the same general order as that reported by other investigators for commercial milk. The rate of loss of ascorbic acid from milk processed during the period that the brass pump was being used was the same as that of milk processed while the stainless steel pump was used. Furthermore, in a study of the oxidized flavor of milk no difference was detected in the flavor of milk that passed through the brass pump and that processed while the stainless steel pump was installed in the equipment. Hence, it appears that the brass pump was not an important factor in causing the destruction of ascorbic acid during the processing of milk.

It is evident from the data assembled here that there is a wide variation in the ascorbic acid content of commercial pasteurized milk even if two bottles of milk should be selected from the same lot of pasteurized milk. The average values, 15.4 and 6.4 mg. per liter, indicate that the last portion of milk through the equipment contained nearly two and a half times as much ascorbic acid as the first portion. These values are not applicable to milk consumed by the public since the ultimate consumer cannot obtain milk as soon as it is processed. However, the corresponding values for the milk after it had been in the refrigerator for forty-eight hours were 6.5 and 3.5 mg. per liter, indicating that the last milk through the equipment contained nearly twice as much ascorbic acid as the first milk.

Considered from a practical standpoint, the stability or rather the loss of ascorbic acid is identical for the raw milk taken from the stainless steel vat just before and for the hot milk taken from the vat immediately after pasteurization was completed. It is apparent from the results reported here that the ascorbic acid present in the milk taken at the four stages of processing is very unstable and that it is rapidly lost from milk stored in darkness at 10° C. under conditions similar to those of many homes. These results add further evidence of the need for replacing the excessive loss of ascorbic acid during the commercial processing of milk. This is particularly true when milk constitutes a major portion of the diet as in infant feeding. In an earlier paper[11] it was suggested that modified commercial milk could be quickly, easily, and quantitatively enriched by adding a standardized, rapidly disintegrating ascorbic acid tablet to the nursing bottle as the milk is being warmed for the infant's meal.

SUMMARY

Mixed herd milk was pasteurized on a commercial scale by the holding method, in typical dairy plant equipment. At twenty-two intervals during the school year samples were collected at four stages of processing; namely, a sample of the thoroughly mixed raw milk, a sample of the hot milk as soon as pasteurization was completed, a sample of the first milk through the cooling and bottling equipment, and a sample from the last milk through the equipment. The stability of the ascorbic acid was determined by assaying the various samples initially and at twenty-four-hour intervals during

ninety-six hours storage in darkness at 10° C. The amount of ascorbic acid varied widely for milk at different stages of processing. The stability of the ascorbic acid was low, and milk taken at all four stages of processing lost ascorbic acid very rapidly during storage in a home-type electric refrigerator. Thus, when milk constitutes the major portion of the diet as in infant feeding, it should be accurately enriched with ascorbic acid.

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THE LAURENCE-MOON-BIEDL SYNDROME

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THE combination of features, which together make up the condition known as the Laurence-Moon-Biedl syndrome, appears to be an uncommon one. In the 1860's Laurence and Moon first described this condition as an association of retinitis pigmentosa with polydactylism. Six cardinal features make up this unusual and interesting syndrome. These are (1) obesity, (2) retinitis pigmentosa, (3) mental retardation, (4) genital hypoplasia, (5) familial occurrence, and (6) polydactylism, listed in the order of frequency. Reilly and Lisser[2] analyzed seventy-three cases and mentioned that in only twenty-five of these was the complete syndrome present. Other anomalies may occur in this condition; these have been described as syndactyly, hypertension, oxycephaly, cataracts, night blindness, and other visual defects. The ocular manifestations are variable and atypical retinitis pigmentosa or chorioretinal atrophy have been reported. In the case recorded here the ocular anomaly is that of an atypical retinitis pigmentosa.

Hassin[1] believes that many cases reported as juvenile amaurotic family idiocy may in fact belong to the syndrome under discussion. This appears to be due to the fact that some of the manifestations of amaurotic family idiocy also occur in the Laurence-Moon-Biedl syndrome. Ritter,[3] however, has not confirmed this assumption by his pathological studies.

The obesity is a constant feature of most of the reported cases. It appears to be unassociated with any increased appetite, differing in this respect from the much more common type of fat child due to excessive food intake. The polydactylism may affect hands and feet, or only one or the other. It is usually postaxial, that is, with the extra digit toward the fifth finger or toe. This polydactylism has a strong familial element. The mental retardation appears to be an inconstant feature of the syndrome.

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CASE REPORT

Clinical History.—M. M., a female child of pure Bantu race, aged 5½ years, was brought to hospital by her parents because she suffered from poor vision. She was admitted to Baragwanath Hospital on June 10, 1950, for investigation.

The father stated that his daughter's sight had become steadily and progressively worse. This poor vision was particularly noticeable in the twilight toward evening. On direct questioning regarding the obesity of the child, the father said that she had been fat since early infancy; he had not noticed any increased appetite, and seemed to think that his daughter did not eat any more than other children. The child was a normal full-term birth but the birth weight was not known. She was breast fed until the age of 8 months. Nothing untoward was noticed except that the baby was fat from early infancy. With regard to the child's milestones of development, such as sitting up, walking, and talking, the parents both insisted that she was backward, and is still mentally backward as compared with children of the same age group.

The child's bowels acted regularly, and there was no abnormality in her micturition history.

Family History.—One brother, aged 2 years 3 months, is quite healthy. The father wears glasses for short-sightedness. He had a brother who died at an early age and who had extra fingers. The maternal grandfather also had extra fingers.

The father and mother are not related.

abdomen, breasts, and thighs (Figs. 1 and 2).

Examination of the hands revealed the presence of accessory fingers on both sides. These were postaxially situated adjacent to the fifth fingers (Fig. 2). There was also a definite widening of the small toe of the left foot.

Fig. 1.

Fig. 2.

Fig. 1.—Photograph showing obesity and distribution of fat.
Fig. 2.—Photograph showing postaxial polydactyly of hands.

Clinical Examination.—The patient was a placid, extremely obese female child.

Her temperature was 98° F., pulse rate 90 per minute, respiratory rate 26 per minute, weight was 66 pounds, height 41 inches.

Compared with children of the same age group, this child appeared to be definitely mentally retarded.

She was extremely obese with the distribution of fat over the whole body but most marked around the shoulders,

Blood pressure, right arm, was 100/60 mm. Hg.

Clinically the heart was not enlarged. There were no murmurs present but the heart sounds appeared distant, due to the thick chest wall.

Breath sounds were faint due to the thick chest wall. Nothing else abnormal was detected.

Examination of the abdomen revealed an extremely fat anterior abdominal wall. Spleen and liver were not palpable.

Pupils were equal and reacted to light and accommodation. Reflexes of upper limbs were all present and equal, and both knee and ankle jerks were present and equal. Plantar reflexes were both flexor. No abnormality of any cranial nerve was detected.

Ophthalmological Examination.—A report by Dr. A. I. Friedmann, Ophthalmologist, reads as follows: "Fundi: There is a definite pigmentary disturbance; the pigment being confined to the choroid and being well outlined by the choroidal vessels. There is definitely no perivascular pigment as in typical retinitis pigmentosa, with the bone corpuscle appearance."

The mother and young brother of the patient were both examined by the ophthalmologist who reported them to have normal eyes.

While the patient was in hospital, it was very noticeable that she had extreme difficulty in seeing in the twilight and was often seen being led around by other ambulant patients at this time of the day.

Investigations.—The blood count showed hemoglobin 15 Gm. per cent; white blood cells, 10,000 per cubic millimeter; sedimentation rate, normal. Standard blood Eagle test was negative. Fasting blood sugar was 88 mg. per cent. Urinalysis showed that no sugar, albumin, or acetone was present. No microscopical abnormality was detected. 17-ketosteroid excretion, 1 mg. in a twenty-four-hour specimen of urine. Mantoux test, 1/1,000 dilution tuberculin, was negative; 1/100 dilution tuberculin, negative.

Electrocardiogram showed normal rhythm. No abnormality was shown in the standard leads, V leads 1 to 6 or in the augmented unipolar limb leads.

Radiological examination: The x-ray of the skull showed a calcification of the falx cerebri, which does not have any particular significance (Fig. 3). The pituitary fossa was normal in size and shape, and its bony contours were intact. X-ray of the chest showed the heart to be normal in size and shape, and no abnormality of the lung fields or bony thorax was shown. The radiological pictures of the hands showed six fingers on each side. On the right side, the supernumerary finger was composed of a proximal phalanx and articulated with a bifid fifth metacarpal bone. On the left side the extra finger was made up of underdeveloped terminal, middle, and proximal phalanges. The fifth metacarpal bone was slightly larger than one might expect. There were seven carpal bones present, which might indicate some advancement in bone age. (Fig. 4.) The x-rays of the feet showed only two phalanges of the fifth toe on the right side. On the left side the little toe showed two sets of middle phalanges articulating with a proximal phalanx, with no skin division between them. (This confirmed the clinical observation noted, of the widening of the fifth toe of the left side.) The medial

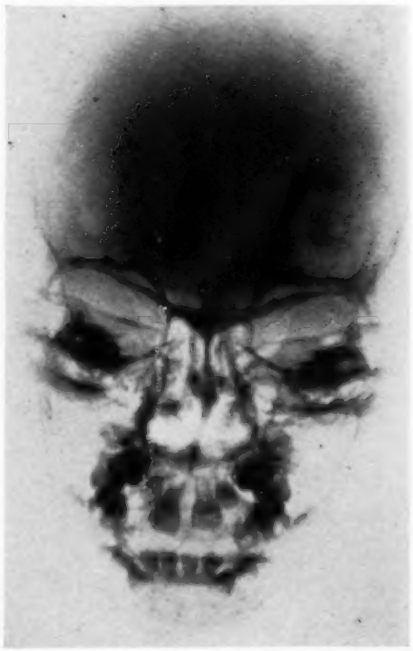

Fig. 3.—X-ray of skull showing calcification of falx cerebri.

Fig. 4.

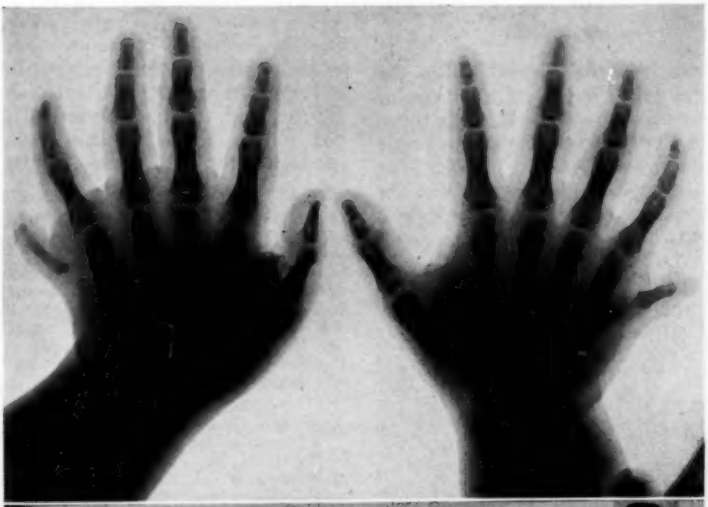

Fig. 5.

Fig. 4.—Radiograph of hands showing polydactylism. See text.
Fig. 5.—X-ray of both feet showing anomalies of phalanges. See text.

phalanx of the double set articulated with the distal phalanx. The terminal phalanges of both fourth toes were underdeveloped. (Fig. 5.)

DISCUSSION

The case recorded here fulfills the diagnostic criteria for an example of the Laurence-Moon-Biedl syndrome, and is the first reported case to occur in the pure South African Bantu. The typical obesity is present, with the child's weight at 66 pounds as compared with an average normal weight for a child of this age of 42 pounds. An atypical retinitis pigmentosa is present in this patient. Although difficult to assess accurately, this child definitely showed a certain degree of mental retardation. With regard to the familial occurrence of this syndrome, this patient has polydactylism occurring on both sides of the family tree. One cannot assess hypogonadism in a girl of this age, although here the low urinary 17-ketosteroid excretion possibly points to a hypopituitarism, which has been mooted as a possible etiological factor in this syndrome. (Normal excretion is 4.4 mg. daily as quoted by Stewart and Dunlop.[4])

SUMMARY

An almost typical case of the Laurence-Moon-Biedl syndrome is reported. This is the first recorded example occurring in a pure South African Bantu, and the patient is a 5½-year-old female child. A short survey is made of this interesting syndrome.

I wish to thank Dr. J. D. Allen, Medical Superintendent, Baragwanath Hospital, for permission to publish this case. I am indebted to Dr. J. C. Gilroy for very excellent photographs, to Dr. A. I. Friedmann for ophthalmological reports, and to the Radiological Department, Baragwanath Hospital, for the x-ray films. Finally, I must thank Mr. A. E. Tomaselli for the x-ray reproductions.

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POLIOSIS

Report of a Case in a Ten-Year-Old Boy

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THE term "poliosis" is derived from the Greek root meaning "gray." It is used to indicate areas of localized depigmentation of the hair in contrast to the term "canities," which is employed to describe the graying or whitening of the hair of the entire scalp.

The case report that follows is of possible interest both to pediatricians and dermatologists because of the rather uncommon occurrence of the poliosis and because of the disappearance of pigment from the hair of the subject at a comparatively early age.

Poliosis represents a dominant trait. We were unable to trace or to find evidence of poliosis in any member of the subject's family for three generations, although premature graying in the paternal grandmother is said to have occurred very early in life.

A review of the literature for the past two decades discloses only a few reported instances of poliosis in children. In this paper no attempt has been made to hypothesize upon the causes for graying of the hair normally or prematurely. The interested reader is referred to the excellent dissertation on the subject by Frost[1] with its bibliography of recent investigation and animal experimentation.

REVIEW OF THE LITERATURE

In reviewing the literature, one is impressed with the large number of etiological factors held possibly responsible for pathologic graying of the hair. Many of the causes suggested are obviously speculative; in any case, the causes have never been demonstrated. Among predisposing factors mentioned are extreme psychotic and psychotic neurotic states, and cerebral trauma. Too, heredity, emotional strain, endocrine disturbances, dietary deficiency, and chronic diseases, as, for example, tuberculosis, syphilis, malaria, diabetes, Addison's disease, and Simmond's disease are considered possibilities. Frost declares it to be the consensus among nutritionists that the graying of fur or feathers may be brought about in many species of animals, usually during the stage of growth, by imposing deficiencies of certain specific mineral elements or factors of vitamin B complex. He adds, however, cautiously, "Sufficient experimental evidence is not at hand to evaluate all of the various possible causes of graying in man."

In this connection a recent publication by Goldman[2] is timely. In fourteen reported instances of acquired and transient changes in the color and growth of hair in children, Goldman stresses their similarity to cases observed in the tropics as part of severe nutritional disturbances, although in lesser degree. Further, Goldman found that the systemic factors more commonly associated with but not necessarily causal for the cases in the Cincinnati area were intestinal parasitism, especially infection with oxyuris. Four children had hair changes associated with sulfonamide medication. These began in the first week after sulfonamide therapy. In view of the antagonistic inhibitory therapeutic effect of the sulfonamides to para-aminobenzoic acid, it would seem logical that the internal use of sulfonamides might possibly interfere with the proper utilization of PABA and closely related derivatives of impor-

tance in metabolism and possibly in the growth and proper physiology of the hair. Goldman believes that his series of patients was definitely benefited by systemic therapy with Panthenol* (alcohol of pantothenic acid) in large doses, which appeared to help in accelerating regrowth and return of the normal color of the hair.

Kolew[3] reported the case of a girl whose hair turned gray prematurely. Twelve years of age, she was the seventh and youngest child of a family in which all the members, including grandchildren, were absolutely normal. There was no infectious disease, no trauma; the child was normal in every respect. Seventy per cent of the hair of the scalp was gray, the rest was of a dark, chestnut brown color. Microscopic examination of the affected hair showed complete absence of pigment, but no fungus. Kolew attempts to explain premature grayness in his patient by biologic process. He thinks that since at conception, the father was aged 60 years, and the mother 50, with their hair already turned gray, the premature grayness of hair in the child was due to the partial incompetence of their embryonic systems.

Hollander and Schmitt[4] submitted a series of group pictures, photographs of children aged 4 and 5 years, respectively. These photographs of children and their father seem to illustrate a hereditary causation for depigmentation of the hair in localized areas of the scalp and of the skin. The location of the canities was the same in the daughters as in the father, and the vitiliginous areas on the bodies of the children corresponded, too, rather closely to his.

Hare[5] was able to trace six generations of premature grayness in the hair. The abnormal persons showed no signs of the abnormality until they reached the age of 17 or 18 years, at which time the hair then slowly turned white so that by the age of 25 or 26 years, it had completely lost its color.

Nicholls[6] reports seeing several children in Malaya aged 5 to 12 years (two were of the Malayan race and the other Tanrils), ill-nourished, in which graying of the hair occurred. Improvement followed on a good diet, including eggs, milk, and fruit. Many of these children had been living largely on manioc root. In addition to graying of the hair, they showed many vitamin deficiencies.

*Hoffmann-La Roche, Inc.

CASE REPORT*

R. S., a 10-year-old white boy, was first seen on March 22, 1951, because of two separate patches of gray hair which the mother discovered accidentally during August, 1950, while she was combing his hair. Since the first few gray hairs were first noticed, the child's scalp has been watched carefully. The depigmented hairs have increased in number so that at present they are represented by two distinct patches.

Family History.—The paternal grandmother is said to have "grayed" very early in life; otherwise the family history is irrelevant.

Past History.—The patient was a full-term infant. Birth weight was 7 pounds 12 ounces. He was breast fed until the age of 4 months and threve nicely upon breast as well as upon artificial feedings. His first tooth appeared at the age of 7 months, and he had eight teeth at the end of one year. He sat up alone when he was 4 months of age, walked and said a few words at the end of one year. He had measles at the age of 6 years (1946), chicken pox at 7 years (1947). There were no sequelae. He was immunized against whooping cough, scarlet fever, tetanus, and diphtheria. He received a vaccination against smallpox at the age of 3 months. He has always been a healthy infant and child. The patient has hay fever and has experienced episodes of sneezing during the spring of the year. There is no history of medication of any kind. The diet was always a well-balanced one with sufficient vitamins A, B, C, and D. Vita-

*Patient presented before the Philadelphia Dermatological Society, April 20, 1951.

mins A and D were supplemented during infancy and early childhood by the usual customary pharmaceutic preparations.

History of Present Condition.—As has already been stated, the gray hairs were discovered by chance during August, 1950. The number of gray hairs increased so that at the time the boy was seen these were represented by two distinct patches.

Physical Examination.—A well-nourished, healthy school boy with a keen mentality. Height 57¼ inches, weight 96 pounds. Twelve pounds overweight according to age-height. The remainder of the examination including the heart, lungs, abdomen, etc., is negative. There is no evidence of other abnormalities and no evidence of vitiligo. Upon examination two patches of graying hair are seen: (1) upon the left temporal-parietal area of the scalp; (2) upon the right occipital region. These cover an area approximately 5.08 cm. (2 inches) by 1.3 cm. (½ inch). The individual hairs are not atrophied and retain the characteristic luster. There was no evidence of any associated seborrhea of the scalp. The hairs do not break when extracted by means of a forceps and no areas are suggestive of tinea capitis. The following laboratory reports were taken on April 7, 1951: Blood count—hemoglobin 10.5 Gm., red blood cells 3,450,000, white blood cells, 7,400, neutrophils 49 per cent, lymphocytes 50 per cent, eosinophils 1 per cent. Urinalysis: color, light straw, clear; reaction, acid; specific gravity, quantity insufficient; albumin, negative; microscopic, some white blood cells; sugar, negative; acetone, negative; amorphous phosphates, some. Blood chemistry, urea nitrogen, 15 mg. per cent, glucose 150 mg. per cent; total cholesterol, 220 mg. per cent. Blood serology, Kahn test, negative.

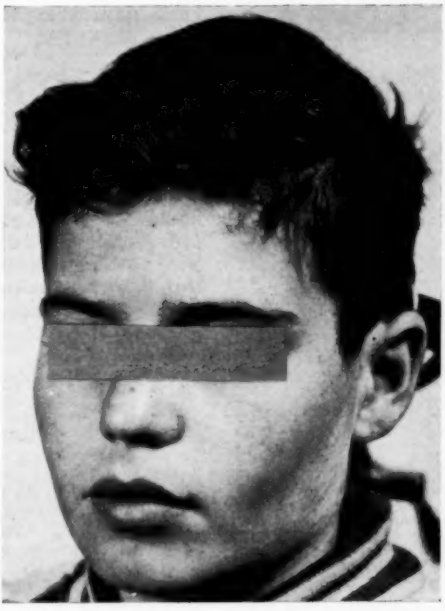

Fig. 1.—Note the patch of gray hairs upon the left frontal region of the scalp.

Because of the abnormally high glucose reported on the first examination, a fasting blood sugar was taken on July 2, 1951, and reported 100 mg. per cent.

On April 20, 1951, several of the hairs from the gray patch as well as normal hairs from the uninvolved areas of the scalp were extracted and submitted for examination to Dr. Albert M. Kligman, mycologist, of the Department of Dermatology, at the University of Pennsylvania. Culture upon Sabouraud's medium failed to demonstrate growth of fungi. The McManus stain for fungi was also negative. Microscopic examination of a gray hair and a normal hair from the scalp of the patient was made (Fig. 2). It will be seen that the nonpigmented hair is almost transparent, the medullary canal being devoid of pigment as compared to the normal hair of the same child.

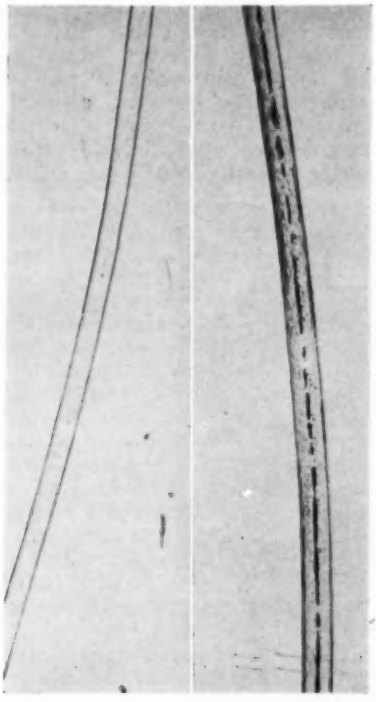

Fig. 2.—Photomicrographs of nonpigmented and normal hairs from patient's scalp. Note the almost complete translucency of the nonpigmented hair as compared to the normal pigmented hair.

MANAGEMENT

Calcium pantothenate 0.006 Gm. (1/10 gr.) was administered once daily. When the patient was re-examined one month later, there was no obvious improvement. The treatment is being continued.

SUMMARY

A 10-year-old white boy showing partial hereditary poliosis, which apparently manifested itself suddenly, is reported. Except for the presence of abnormal blood glucose, the physical examination was entirely negative. The patient is receiving calcium pantothenate per os daily. To date there has been no obvious improvement in his condition.

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POTASSIUM BROMATE POISONING

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THE first report of "a case" of potassium bromate intoxication appeared in the literature in 1941.[1] Dunsky[2] in 1947 reported a fatal case of a 17-month-old boy who had ingested an unknown quantity of a "neutralizer" from a home permanent set. Thompson and Westfall[3] in 1949 reported a nonfatal case in a 2½-year-old male due to similar circumstances. Later in the same year Kitto and Dumars[4] reported three nonfatal cases from ingestion of "neutralizing solution" of permanent wave sets. Robertson, Flothow, and Kissen[5] reported a nonfatal case of a 14-year-old white girl who also ingested a "neutralizer solution." The last nonfatal case, a child aged 3 years, was reported in the British literature by Parker and Barr[6] in 1951 to bring the total cases reported, to date, to eight with one fatality. The cases herein reported represent the ninth and tenth known reported cases.

CASE REPORTS

Case 1.—M. D., white male, aged 2 years, drank one-half glass of neutralizer solution* but fifteen minutes later vomited once. One hour after ingestion his stomach was lavaged at an emergency room in a local hospital and then he was sent home. Diarrhea and vomiting continued, and four hours after ingestion he was admitted to St. Francis Hospital, Aug. 11, 1949.

Examination on admission revealed him to be listless, lethargic, and pale. Temperature was 101° F. (rectally) but pulse and respiration were good. Several liquid stools were passed soon after admission. Intravenous fluids were started but, because of restlessness, had to be discontinued in favor of subcutaneous fluids.

Twelve hours later (August 12) there had been very little absorption of the M/6 lactate solution. He was markedly dehydrated, eyes were sunken in the orbits, skin was clammy and dry, turgor was poor but there was no cyanosis. Oxygen was started. The superficial veins were collapsed; therefore a "cut down" was done and the great saphenous vein was cannulated. Intravenous fluids were given as follows: 500 c.c. M/6 lactate solution; 500 c.c. Amigen solution; 1,000 c.c. 5 per cent dextrose in distilled water. See Table I for further laboratory findings.

On August 13 the skin turgor was good and he looked much better. Oral fluids were begun. The following day regular diet was resumed and he continued to show rapid improvement until discharged from the hospital on August 16 or five days after admission. He remained afebrile after the first thirty-six hours. Subsequent follow-up has failed to show any residual findings of the kidney damage.

Case 2.—K. R., white female, aged 20 months, drank an unknown quantity of neutralizer* on March 16, 1950. Within ten minutes she began vomiting. Her mother gave her milk as an emetic. She was instructed to take the child to the emergency room of St. Francis Hospital where gastric lavage was done and one pint of soda water was left in the stomach. In addition 1 Gm. of sodium thiosulfate was given intravenously as an antidote. She was then admitted to the hospital and given 1,000 c.c. 5 per cent dextrose in distilled water the first night intravenously. The laboratory reports the following morning and succeeding days are given in Table II.

On March 17 she looked ill but had a temperature of 100.0° F. (rectal).

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*(Toni) Home Permanent.

*Richard Hudnut.

TABLE I

DATE	NPN	BLD CO_2 VOL. %	RBC	HB.	WBC	DIFFERENTIAL				URINALYSIS					
						SEG.	LYM.	B.F.	MON.	ALB.	SUG.	WBC	CASTS	EPITH. CELLS	BLOOD
8/12/49	51 mg. %	51.5	4.72	14.2	8,500	52	32	15	1	2+	–	Occ.	Many		
8/13/49	41.4		3.900	11.3	7,500										
8/14/49										Neg.	–	Neg.	Neg.	Occas.	
8/15/49										Neg.	–	Many with clumps	Neg.	Rare	
8/16/49															

TABLE II

DATE	NPN	BLD CO_2 VOL. %	RBC	HB.	WBC	DIFFERENTIAL				URINALYSIS					
						SEG.	LYM.	B.F.	MON.	ALB.	SUG.	WBC	CASTS	EPITH. CELLS	BLOOD
3/17/50	36.3		3.61	12.0	13,900	68	30	2		+	+	8-10	Rare hyaline		
3/18/50	33.9	40.8								–	–	8-10	2 gran. 1 hyaline	3-6	
3/19/50										Tr.	–	15-25	1 gran.	5-10	
3/20/50	32	37.5										30-40 With clumps	Rare hyaline	2-3	4-6 APF
3/21/50										Tr.	–	4-6		1-3	0-2

She was given 500 c.c. M/6 lactate solution and 500 c.c. 5 per cent dextrose in distilled water. The following day she looked better but another 1,000 c.c. of intravenous fluids were given.

On the third hospital day she developed definite oliguria. Her temperature was 101° F.; therefore 500 c.c. of intravenous fluids were given.

By the fourth day her temperature was normal; urinary output was improved. She took 1,800 c.c. oral fluid and had a measured output of 1,000 c.c. plus several wet diapers during the night.

She was discharged on the fifth day, March 21, having slight urinary findings as above illustrated. One week later the urine was completely negative. She made an uneventful recovery.

DISCUSSION

These cases both represent the prompt development of gastrointestinal effects from potassium bromate poisoning in the human race. In addition, both cases developed varying degrees of kidney damage as evidenced by the clinical and urinary findings. The gastrointestinal effects are caused by the reaction of bromate and hydrochloric acid in the stomach resulting in caustic action of hydrobromic acid and free bromine. The renal damage is caused partially by the products of hemolysis and also by the oxidizing effects of bromate ion of the renal tubules.[7, 8] The slow and prolonged renal excretion is probably a direct cause of the acute and subacute nephritis.[3] Dunsky's case revealed a predominance of tubular lesions while the glomeruli were not involved.[2]

After the Toni Company's research pharmacologist Michael[9] suggested an antidote, the initial treatment of these children was modified to include other than symptomatic and supportive treatment. He suggested that the stomach acidity be neutralized to prevent the formation of the irritating hydrobromic acid and that a sodium salt be used to counteract the "toxic effects of potassium ion or substitute sodium bromate for potassium bromate." He suggested the use of sodium thiosulfate to combat the oxidizing effect of the bromate ion. The second patient, K. R., was given sodium thiosulfate intravenously since it had been mentioned in the literature subsequent to the other case, M. D., reported above.

Brunner[10] lists the following procedures for immediate and follow-up treatment of these individuals who have accidentally been poisoned.

1. Administration of an emetic.
   (a) Mustard powder, 1 teaspoonful, in 300 c.c. of warm (not hot) water or
   (b) Zinc sulfate, 1 teaspoonful, in water, followed by copious ingestion of water, or
   (c) Apomorphine, 5 mg., intramuscularly,
   (d) Gastric lavage.
2. Sodium thiosulfate, 1 level teaspoonful in water. This may precede but should in addition always follow the emetic.
3. Demulcent drinks, such as milk, flour and water or cereal gruel.
4. Sodium thiosulfate solution, 1 per cent by intravenous drip, in quantities of 100 to 500 c.c. If not feasible 10 to 50 c.c. of 10 per cent solution of sodium thiosulfate solution may be given intravenously.

Brunner stated that gastric washings and urine should be tested for the presence of bromide. Since a fatal outcome is apparently dependent on the nephrotoxic effect of bromate, speedy removal of the material from the stomach by mechanical or chemical means is of great importance. Uremia should be treated as for mercury poisoning.

"The neutralizing substances have been changed in the last year by one manufacturer (Toni Company). They now use sodium perborate and sodium hexametaphosphate. These have a much less toxic reaction than bromate. When antidotal procedures are required in a case of perborate ingestion, those listed under heading one may be used. In addition, the administration of magnesium sulfate by mouth is suggested."[10]

SUMMARY

1. Two cases of bromate poisoning due to accidental ingestion of a neutralizing solution have been reported. Both children recovered completely after a brief period of supportive care in the hospital. One child was given sodium thiosulfate as an antidote and seemed to have a less toxic course in the hospital.

2. Brief mention of the toxopharmacological action for bromate on the gastrointestinal tract and renal system is restated.

3. Re-emphasis of Brunner's suggested immediate hospital treatment of these patients is made in an attempt to help the profession counteract the deleterious effects of bromate intoxication.

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Erratum

In the article by Dr. Albert B. Sabin entitled, "Transmission of Poliomyelitis Virus," in the November, 1951, issue, the second sentence, page 519, should read:

When the confusion resulting from this "know-nothing" conclusion forced a recent conference to formulate some sort of statement about the mode of transmission, the following was said:

Medical Progress

PITYRIASIS ROSEA IN CHILDREN

A Review of the Literature and a Report Upon Several Cases Demonstrating Clinical and Histopathologic Features of the Dermatosis in White and Negro Children

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THIS review is presented for two reasons; first, because the clinical manifestations of pityriasis rosea, a dermatosis unfamiliar to many pediatricians, needs to be brought to attention; and second, because this dermatosis, supposedly uncommon in children, is really of rather frequent occurrence, particularly in the early spring and fall seasons of the year.

The winter and spring of 1951, both in New York and Philadelphia, were noteworthy for the many virus infections encountered by both the general practitioner and the pediatrician. Among such infections, those involving the upper and lower respiratory tract were quite frequent. If many dermatologists are correct in their opinion that pityriasis rosea is of virus etiology, and transmitted through the tonsils and lymphatics of the upper respiratory tract, it is not surprising that this dermatosis appeared either simultaneously with or quite independently of infection of respiratory organs. However, because of the mildness of the infection, or because of the frequency with which antibiotics and sulfonamides are administered, it is our opinion that pityriasis rosea in a large number of patients was regarded as a development secondary to such therapy or else the bizarre rash in its milder manifestations was overlooked completely. Accordingly it is hoped that this paper will serve a use in making the pediatrician more mindful of the possibility of pityriasis rosea by familiarizing him with the clinical picture of the disease.

The term pityriasis rosea is derived from the Greek-Latin word "pityriasis" meaning scale, and "rosea" meaning pink. With the exception of the herald patch which precedes the generalized eruption by approximately a week or more, the early lesions vary considerably, there being several varieties of the disease which are often confusing and misleading to the uninitiated. The herald patch itself is frequently mistaken for that of tinea corporis, and understandably so for the lesion is definitely circinate and grossly resembles that of tinea circinata. The differential diagnosis will be discussed later, including that of tinea circinata.

CLASSIFICATION

In children, as well as in adults, there are two dominant types of pity-

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riasis rosea, the macular and the papular. (Recently, we have seen a vesiculopapular form of pityriasis rosea in a Negro girl, B. S. in this report, whose case will be discussed in detail later.) Klauder[1] has pointed out that the papular (follicular) and maculopapular eruptions are more frequently seen in the Negro race, as have Butterworth[2] and Corson.[3] The following classification by Klauder[1] is useful from a practical point of view:

- **Macular**
  - Punctate, Guttate, Nummular, Circinate
    - Bilateral, Unilateral, Generalized, Confluent and Diffuse
      - Pityriasis Gigantea (Darier)
      - Pityriasis Circiné et Marginé (Vidal)
- **Urticarial**
  - Pityriasis Rosea Urticata (Vorner)
  - Urticé Pityriasis Rosea (Hallopeau)
- **Papular**
  - Maculopapular
  - Follicular
  - Miliary
    - Large
    - Small
- **Vesicular**
  - Pityriasis Rosea with Vesication

HISTORICAL

Pityriasis rosea was first described by Gibert in 1860 but his descriptions applied only to the macular type. In the United States, Louis Duhring is credited with the first desription of pityriasis rosea.

AGE INCIDENCE

The age incidence has been tabulated by different investigators with results more or less uniform. Graham Little*[4] saw 6.7 cases per thousand in a dermatologic clinic for adults and children and 4.7 per thousand in a children's clinic. In Thomson and Cuming's[5] series of cases, although one patient was 77 years old, most of the patients were from 6 to 15 years of age. Savill in a discussion of Little's[4] paper stated that her patients ranged from 11 months to 50 years. Adamson's[6] patients ranged from 2 to 60 years, the majority being from 15 to 30 years.

Klauder[1] states that pityriasis rosea is rarely seen in infants, is uncommon in children and in the aged. The frequency with which we have seen pityriasis rosea in children during the past few years in out-patient dermatological departments, both in New York and Philadelphia, suggests that perhaps this dermatosis is decidedly more common today than it was three decades ago. Perhaps, as Greenbaum[7] suggested in 1941, the clinical picture of pityriasis is changing as it is difficult to believe that the older dermatologists would have failed to observe oral lesions of pityriasis rosea had they been present.

Highman and Rulison[8] in an analysis of fifty-two cases found two in children of 4 years, one in a child 7 years, and in a child 10 years of age. In Howard Fox's cases of the disease, one

*Quoted by Niles and Klumpp.[11]

case occurred at the age of 17 months, one at 20 months, one each at the ages of 8, 9 and 10 years. Thomson and Cumings[5] in a total of 156 patients found four males and one female between the ages of 1 and 5 years, fifteen males and fifteen females between the ages of 6 and 10 years, and fifteen males and seventeen females between the ages of 11 and 15 years. Percival[9] tabulated the age incidence of pityriasis rosea for various age groups. The following represents statistics of various investigators as gathered by him:

Investigator	6-10 yr.	10-20 yr.	20-30 yr.	30-40 yr.	40-50 yr.	50-60 yr.
Little	22%	44%	---	---	---	---
Weiss (324 cases)	54	91	124	24	30	1
Towle (198 cases)	21	43	77	46	11	---
Highman (51 cases)	4	6	13	21	3	4
Fox (74 cases)	5	15	35	9	10	---
Edinburgh (234 cases)	29	76	80	31	17	1
Moingeard	41 out of 56 between 15 and 35 years.					
Szaboky	87 out of 119 between 15 and 40 years.					
Thieberge	Occurs between 15th and 35th years.					

Weiss, Lane, and Showman[10] in a series of 379 cases (age not stated in one case) found an incidence of 14.2 per cent between 0 and 10 years. The youngest case was an infant 8 months old. Niles and Klumpp[11] in their series of 153 patients found 3.27 per cent were less than 10 years old. Their youngest patient was 5 years old. These investigators state that Pernet found pityriasis rosea more frequently in children than in adults. They state that the youngest patient reported in the literature was one, aged 7 months, of Crocker's, one-third of whose patients were children. Leiner reported pityriasis rosea in a child of 21 months; Savill's youngest patient was 11 months old; Little's, 18 months; Thomson and Cumings', 21 months; and Adamson's, 2 years. Lord's son, aged 3 years, and Haas' baby had typical pityriasis rosea. Finnerud's youngest patient was 5, Saad's 10, Kogoj's and Farkas' 9 years old.

SEX INCIDENCE

Highman and Rulison[8] found thirty females and twenty-two males in fifty-two cases of pityriasis rosea analyzed. Weiss, Lane, and Showman[10] found a ratio of two females to one male, and this is maintained by Towle, Thieberge, Moingeard, and Adamson. On the other hand, Graham Little, Crocker, and Cunningham found that their cases occurred with equal frequency in the two sexes.

RACIAL INCIDENCE

As to race, pityriasis rosea is usually seen in white persons, but the disease is by no means limited to them. Weiss,[12] Gross,[13] Stillians and Benedek,[14] and Schiller[15] have reported pityriasis rosea in Negroes. Schamberg,[16] in a discussion of Friedman's[17] paper, reported a case of pityriasis rosea in a mulatto. Of 380 patients seen in St. Louis by Weiss and associates, 24.2 per cent were Negroes. On the other hand, Niles and Klumpp's series of 219 patients had only two Negroes. While exact statistics from

their experience in a large out-patient practice are not available, we are convinced that both at the Flower and Fifth Avenue Hospitals and The Metropolitan Hospital, New York, where a large percentage of patients seen are of the Negro race, pityriasis rosea is not at all an uncommon dermatosis.

SEASONAL INCIDENCE

It is generally agreed that most cases of pityriasis rosea are seen during the early spring and fall. This is sustained by the study of Weiss, Lane, and Showman[10] who found the highest incidence in the spring and the fall. The fewest cases occurred in June and July. On the other hand, other investigators have found the highest seasonal incidence during the winter months. Niles and Klumpp state that seventy-eight (38 per cent) of their 203 cases started in the fall, fifty-nine in the winter, thirty-eight in the spring, and twenty-eight in the summer.

ETIOLOGY

Most dermatologists are inclined to regard pityriasis rosea as a mildly contagious disease. In all probability it is due to a virus which enters through the upper respiratory tract, although the virus nature of the disease has never been established definitely. In this respect it is regarded very much as a mild exanthem seen in early childhood, such as German measles and chicken pox. There is no proof that this dermatosis is due to a streptococcus. A small number of cases are apparently due to contact with other patients. Transference of the disease by inoculation with material obtained from active lesions or organisms obtained by culture have failed with the exception of the experiment reported by Udo Wile.[18] Wile attempted for about two years to transmit the disease to members of his staff and to medical student volunteers by implanting scrapings of the initial plaque of the secondary lesions into the skin of the flank by scarification, but failed. Then he rubbed the blister contents into a scarified area of the skin or injected it just below the epidermis. In three cases, the subepidermal injection of the blister fluid of the primary plaque and the secondary patches of pityriasis rosea did result in a generalized eruption in many ways resembling the eruption of pityriasis rosea. Vaccination with the same material resulted in a similar generalized eruption in a single case. It was from these experiments that Wile concluded that the transmissability of the disease points to an infectious agent which is present in some form in the local lesions.

Thomson and Cumings[5] in their summary suggest that the cause must be looked for among filter-passing organisms. Although Wile states that sporadic cases appear constantly during the summer and winter months in increasing numbers, and there is no season when they do not occur, the majority occur during epidemics in the spring and fall. A change in the outer clothing and underwear during the spring and fall seasons is thought to be a factor in the etiology.

Hazen[19] believes that focal infection (tonsils) may be a source of the infection, but that the portal of entry may be through other lymphatic structures in the throat. However, from the literature, it does not seem that most dermatologists concur in this view. Interesting is the fact that lesions of pityriasis rosea have followed the intramuscular injection of bismuth

subsalicylate, at least they are not unlike an intense and prolonged pityriasis rosea in eighteen adults observed. The eruption disappeared after the bismuth injections were discontinued. Reiss[20] reported the case of a girl aged 3½ years which developed ten days after her being injected with diphtheria toxin-antitoxin. This investigator felt that the DTAT played the part of an indirect biotropic agent, not a specific one, and that the external infection thereafter was responsible for the development of the eruption. Highman and Rulison[8] are of the opinion that pityriasis rosea is undoubtedly an infectious disease. They base their argument of a generalized infection on the occasional presence of such constitutional symptoms as fever, malaise, and slight arthralgia. However, against the theory of a generalized infection stands the absence of an exanthem. Other investigators, reporting the simultaneous appearances of pityriasis rosea in two members of the family, offer this finding in support of the infectious theory. This too was the experience of Lord[21] who reported the simultaneous appearance of pityriasis in two members of his own family, in his son, a typical generalized pityriasis, and in his wife, a typical herald lesion. Lord, in a review of the literature, cites eighteen instances of pityriasis occurring apparently as the result of close association with others having the infection. Lord presents the following evidences as supporting the infectious theory:

1. An immunity is conferred by one attack. This fact is generally accepted, although instances of a second attack are on record.

2. Many writers consider the disease to be epidemic.

3. A number of instances, as cited in the literature, occur in members of a family simultaneously.

4. There are several isolated reports of the apparently infective nature of the disease, and, finally, Wile's success in producing by inoculation an analogous eruption.

Since Lord's report, Miller[22] has reported three cases of pityriasis rosea in members of the same family. These cases developed within six weeks and in no case had the patient worn any new, unlaundered clothing or garments which had been stored for a considerable period; further, tonsillectomy had been performed in each case. Kurtz and Davis,[23] closely associated with each other as medical students, but not roommates, contracted pityriasis rosea one week after the other. An experimental attempt to transmit the disease by intradermal injection of a heavy suspension of scrapings from culture lesions of the skin of two students having the disease into two healthy human subjects, and into rabbits, failed. Weiss, Lane, and Showman[10] noted the case of a Negro girl patient aged 9 years, whose brother developed pityriasis rosea. There are many other instances in the literature where pityriasis rosea has developed following association, thus evidence is strongly inclined to the infectiousness or contagiousness of this disease.

HISTOLPATHOLOGY

According to Lever,[24] the histologic picture of pityriasis rosea is that of a nonspecific chronic dermatosis. It is characterized by some parakeratosis, small vesicles within the rete malpighii or just beneath the epidermis. There is also present intracellular edema of the epidermis, acanthosis, a lymphocytic infiltration with some

neutrophils in the upper corium, and capillary hyperplasia. Occasionally, the edema present may result in the formation of a few small vesicles within the rete malpighii or beneath the horny layer. (See Histopathologic Section Case 1.)

CLINICAL PICTURE (SIGNS AND SYMPTOMS)

1. *The Primitive Patch.*—This is also spoken of as "the initial lesion," "the herald patch," or "the mother lesion" since it is usually the first clinical sign and usually precedes the generalized eruption by several weeks. Klauder states that in one of Hallopeau's patients the primitive patch preceded by two months the appearance of pityriasis on the trunk. On the other hand, in Friedman and Wright's case, the herald patch located upon the face was followed within three hours by a generalized rash. Usually there is but a single herald patch. However, there may be two or even more. Frequently, the herald patch is overlooked. It may vary in size from a five-cent piece to a silver dollar. In a case reported by Allen,[25] the herald spot was of gigantic size, occupying half the chest wall. It has a gross resemblance to ringworm of the glabrous skin in that the lesion is round or oval-shaped, although lacking the clinical characteristics of ringworm. The border of the lesion is not raised and there is no clearing in the center as in ringworm. Too, there is not the characteristic scaliness of the lesions that is seen in ringworm, and microscopic examination of the scrapings of the scale fails to reveal the presence of mycelial threads. Culture upon Sabouraud's medium is negative for fungi.

The herald patch may appear anywhere upon the body, except perhaps upon the hands and feet. The face is a common site. Pringle[26] reported the primary patch on the penis. In one of our cases (B. S. Case 1), the primary patch appeared upon the right labia majora and preceded the rash upon the trunk by approximately two weeks. Statistics regarding incidence of the herald patch vary widely from 12 to 94 per cent. As Weiss and collaborators[10] state, it is possible that the primary patch exists in many more instances but is overlooked in the hurry of treating a large number of dispensary patients, or is concealed by a dermatitis caused by various irritating applications.

2. *Generalized Eruption.*—The papular type of eruption is especially common in children, particularly Negro children, and in the majority of instances involves the entire trunk, and less frequently the upper and lower extremities. The hands and feet are usually free of lesions. The face is supposedly free of lesions, although experience shows it is not infrequently involved in children. Indeed, recent estimates indicate that the face above the angle of the jaw is involved in 15 per cent of cases.

The other common variety of pityriasis rosea is the macular type. More frequently one sees a combination of both macular and papular lesions, the so-called maculopapular pityriasis rosea in children. The Negro child, B. S., reported by us, showed vesiculopapular lesions especially upon the anterior axillary folds and upon the dorsum of the chest, which became papular, scaly, and eczematized after one week. This is contrary to Klauder's experience, although a number

of dermatologists, among them Little and Colcott Fox, have stressed vesiculation as part of the clinical picture in pityriasis rosea of children. Wile[18] reported a case with pseudovesicles, the papules appearing as though they were superimposed on apparently deep-seated vesicles and upon puncturing and pressure yielded a drop or two of a clear serum. According to Weiss and associates, Foerster has noted especially the appearance of vesicular types of pityriasis rosea in infants and children.

3. *Clinical Course.*—The eruption may reach its height in the course of a few days. On the other hand, the climax may not be reached for several weeks, new lesions appearing while others seem to grow pale and fade out. The rash disappears spontaneously in about six to eight weeks, with an average duration from five to six weeks. However, Weiss reported two cases of pityriasis rosea in which the lesions appeared and disappeared for over three years. In twenty-six control cases reported by Niles and Klumpp, the average duration was 4.7 weeks.

The individual macular lesions are either circinate or oval-shaped, of a pinkish salmon color, with a fine thin crinkled dry scale, which has been compared to cigarette paper. After a short time the scale loosens in the center, but the edges remain attached peripherally. The long axis of the macule follows the lines of cleavage of the chest, and the entire configuration has been likened to an inverted Christmas tree, with the base of the tree directed upward, the apex downward upon the chest, abdomen, and back. Itching is slight in some children, while in others, it is moderately severe. During the height of the eruption, children frequently complain of a burning sensation of the skin. Apart from the mild pruritis, the condition is asymptomatic, except for prodromal complaints of sore throat, malaise, headache. Occasionally, the cervical glands are enlarged and there may be a slight elevation of temperature. Little is of the opinion that general glandular enlargement occurs in most patients. Early, the symmetrical arrangement of the papular lesions upon the upper and lower extremities and the trunk may simulate an "id" reaction.

4. *Distribution.*—Various observers have found that the lesions of pityriasis rosea are limited mostly to the trunk. In 72.2 per cent of 341 cases reported by Weiss and collaborators the lesions were so confined. The dermatosis also involves the upper extremities, the thighs, but seldom the hands, feet, face, and scalp, in older individuals. In order of frequency, other affected areas include the face, neck, shoulder, arms, forearms, hands, axillae, genitocrural parts, buttocks, thighs, legs and soles. Unusual locations in adults are the scalp, eyelids, and penis. Szaboky has reported eruption on the eyelids, Little and Fox, lesions on the penis. Occasionally, the rash may be distributed unilaterally as was shown by Szaboky, Moingeard, Graham Little and Klauder, or localized in the axillae or groin (quoted by G. H. Fox). According to Weiss and associates, "It seems clear that almost any part of the skin may be involved in the eruptive phenomena of pityriasis rosea, although it must be admitted that the trunk is the site of election." On the other hand, Davis and Waldriff,[27] in

a recent communication, have presented evidence that substantiates the clinical observation that the eruption rather commonly occurs on the scalp, face, neck, forearms, and legs. These investigators remark that while there has been no increase in the incidence in pityriasis rosea, yet over the years the disease may well have changed with respect to its distribution over the body to take on a more generalized eruption than it formerly demonstrated. However, these investigators do not discuss specifically pityriasis in children. The incubation period may vary from a few days to a month or more. There is no characteristic blood picture. Eosinophilia and lymphocytosis are frequently seen.

5. *Unusual Manifestations.*—Haxthausen[28] stressed that in children an atypical lesion on the scalp seems to be of diagnostic value. He quotes Adamson-Allbutt and Rolleston[29] and Kumer[30] as being in agreement with him. Kumer expressly remarks that he has never seen it occur in that situation in adults. Haxthausen found seventy-two cases in one year, of which twelve were cases of children under fifteen years; of these no less than eleven presented a distinct eruption on the scalp, while a similar eruption was not found in a single adult. Among the children, only one, a girl of 14 years, presented a normal scalp. Hartman[31] reported the case of a 36-year-old chemist, who showed a rounded somewhat edematous scaly lesion, the size of a quarter, on the nape of the neck and within the hair line.

6. *Oral Lesions.*—According to Greenbaum,[7] Guequierre[32] appears to have been the first to have presented patients before a dermatologic society showing concomitant oral lesions. Within one month Greenbaum observed oral lesions in four patients, the first three of whom presented solitary pinhead-sized, deep red, hemorrhagic macules upon the buccal mucosa in the region of the rear molars. These persisted from several days to one week and then faded away. The fourth patient presented oral lesions so numerous that the case seemed worthy of clinical record. Costello[33] reported a boy of 6 years who had a typical eruption of pityriasis rosea with the herald patch on the right shoulder for three days. The eruption was accompanied with matchhead- to pea-sized, superficially eroded, edematous lesions on the palate, buccal mucosa, the tongue, and the floor of the mouth. The patient's temperature was 101.2° F. by rectum. Costello remarked that Guequierre had made the point that oral mucous membrane lesions were seen more in children than in adults, especially if the eruption was accompanied by fever. One of our patients (B. S.) showed definite vesicular lesions of the entire mouth during the height of the eruption. Guequierre and Wright[34] reported on fourteen patients observed in three years with associated lesions on mucous membranes. Among these was a boy who showed an annular, punctate hemorrhagic lesion on the buccal mucosa and an erythematous segmented or incomplete annular lesion with a definitely raised border on the right side. Isadore Rosen, in discussing Sobel's[35] paper, said that he had observed similar lesions, that is, vesicles on the tongue.

7. *Palms.*—Davis[36] reported the case of a 16-year-old girl with a profuse rash exhibiting the typical characteristics of pityriasis rosea, the le-

sions upon the palms, similar to those of Combes'[37] case, being indistinguishable from secondary syphilis; yet signs for syphilis were absent and the Wassermann reaction was negative. There were no lesions on the soles. Combes'[37] case was of a woman aged 36 years; the eruption of one week's duration covered the palms and backs of both hands, also the feet. Numerous instances involving the palms and soles in adults have been reported.

8. *Pityriasis Rosea With Purpura.*—Hartman[38] reported the case of a 41-year-old policeman on whom the herald patch was of a hemorrhagic nature, a case of interest because of the unusual association of purpura. Theoretically the elaboration of the toxin causing the damage to the vessel walls and resulting in the purpuric lesions was due to the same infectious agent. Because both types of lesions occurred, evolved, and disappeared simultaneously, it is plausible that the cause of the pityriasis rosea and the purpura was identical.

9. *Diagnosis.*—The following points are helpful:

a. A herald patch (primitive patch), which is generally mistaken for ringworm of the skin and which is most often seen upon the trunk, although it may appear anywhere, is the harbinger. This herald patch is not always found, very frequently being overlooked or masked by the results of topical applications. It is round or oval-shaped and usually precedes the generalized eruption upon the trunk by one to four weeks.

b. Mild prodromal symptoms occur, including sore throat, malaise, and nervous irritability. A generalized adenopathy may be present. There may be a slight elevation of temperature.

c. The eruption itself is at first macular or papular, or maculopapular, or vesicular, and is for the most part distributed upon the trunk. In children, the scalp is frequently involved as are also the mucous membranes of the mouth. The individual macular lesion is of a salmon-colored appearance, generally oval-shaped, with a thin, crinkled, cigarette-paperlike scale, the center of which becomes loose, but is firmly attached at the periphery. The free edges of the scale are directed toward the center. The center of the macular lesion may be completely or partly clear, fawn-colored, and surrounded by a rosy ring. The oval-shaped lesions tend to follow the cleavage lines of the ribs. The full-blown rash presents at its height the outline of an inverted Christmas tree, as has already been described.

10. *Differential Diagnosis.*—The important dermatoses with which pityriasis rosea may be confused include (a) tinea circinata; (b) the macular syphilide; (c) psoriasis; (d) disseminated seborrheic dermatitis; (e) lichen planus; (f) scabies.

a. *Tinea Circinata (Tinea Corporis):* Pityriasis rosea is most often mistaken for tinea circinata but is differentiated from it by the herald patch and by the lack of a raised peripheral border to its macular lesions. Ringworm of the glabrous skin spreads peripherally so that there is soon a ring within a ring, the center tending to clear; and scraping of the scale and culture will disclose mycelial threads and fungi upon Sabouraud's medium. The scale in pityriasis rosea is peculiarly thin and crinkled, like cigarette paper. Too, the lesions are

more numerous than those of ringworm, of which seldom more than half a dozen are seen upon the body. As a further contrast, the distribution of ringworm lesions is upon the exposed parts of the body, such as the face and hands, whereas those of pityriasis are generally upon the covered parts, especially the trunk.

b. *Macular Syphilide:* The most important single point differentiating the macular syphilide from the macular lesion of pityriasis is the nonscaliness of the syphilide. Scaling, if present at all in syphilis, is very slight. Too, the macules in syphilis are smaller in size than those of pityriasis and of a reddish brown or copper color. They involve the palms and soles, areas of the skin seldom affected in pityriasis rosea. Macular syphilides involute much more slowly than the macules of pityriasis and infiltrate more greatly. In syphilis, there is frequently a history of infection, a positive blood serology and concomitant signs of syphilis, such as mucous patches, syphilitic rhinitis, enlarged liver and spleen, etc.

c. *Psoriasis:* The scale of psoriasis is characterized by an imbricated mother-of-pearl, heaped-up appearance, which in typical cases renders diagnosis easy. Nevertheless, psoriatic lesions may at times grossly resemble lesions of the macular or papular pityriasis rosea. However, the lesions of psoriasis are more acutely inflamed and are much brighter red than the salmon-colored pink scale of pityriasis rosea. The Auspitz phenomenon (bleeding points), present in psoriasis, is absent in pityriasis. Further, psoriasis is a chronic dermatosis, returning time and again, in contrast to pityriasis rosea, which is generally characterized by a single attack.

d. *Seborrheic Dermatitis:* The greasy, scaly lesions of this seborrheic dermatitis are found over those areas of the skin richly endowed with sebaceous glands, as, for example, the scalp, the eyebrows, behind the ears, the nasolabial folds, the sternum and the spinal column, the umbilicus, the flexures of the extremities and creases of the groin. The condition involutes more slowly than pityriasis. The scales of seborrheic dermatitis are coarser, more greasy, and more abundant.

e. *Lichen Planus:* The violaceous polygonal lesions of lichen planus, which have a predilection for the anterior surfaces of the wrists, the ankles, and the inner sides of the legs, are absent in pityriasis rosea. However, lichen planus is often confused with the papular type of pityriasis rosea.

f. *Scabies:* Scabies is sometimes confused with the papular type of pityriasis rosea. However, the presence of burrows in scabies and their absence in pityriasis is diagnostic. Too, in scabies in children the papular lesions are present upon the abdomen especially surrounding the umbilicus, also upon the elbows, the anterior aspects of the wrists, between the webs of the fingers, and between the toes, upon the buttocks and the thighs. The itching of scabies is characteristic in that it is invariably worse at night. Finally, the presence of scabies among other children, or in members of the family, and the identification of the acarus are conclusive points diagnostically.

11. *Immunity and Recurrences (Recrudescence).*—While most investigators agree that it is exceedingly rare to

find patients who have had two or more attacks of pityriasis, recurrences are nevertheless occasionally met with. Edelston[39] reported the case of a child, aged 10 years, who had typical lesions of pityriasis rosea which cleared in three weeks and who, four years later, developed the primary lesion in the same place as before, with complete eruption following in seven days. Sayer[40] cites two cases: one, that of a white woman, 24 years old, who had a generalized eruption of pityriasis which was cleared up in three weeks by the use of Alpine therapy and who four years later developed a typical generalized eruption, which again was cleared in three weeks by means of the Alpine lamp; second, that of a white woman, 18 years old, with an extensive eruption of pityriasis rosea in which the Alpine lamp treatment was employed, who years later required treatment for another attack. In his report, Sayer mentions Klauder's case presented before the Philadelphia Dermatological Society in 1928, and also a case presented at the New York Academy of Medicine by Feldman in 1931, these both being cases of two attacks of pityriasis rosea in a patient. Allen, in a discussion of the paper by Weiss and associates,[10] claims to have seen the disease recur seven times in a patient. Sherwell saw the disease in the same patient at two successive pregnancies. Zeisler, in a discussion of the same paper, said that he personally had pityriasis twice. Sayer insists that it is important to differentiate between a recurrence and a recrudescence; suggesting that it is best to set an arbitrary time limit of one year between the attacks in order to classify another eruption as a recurrence. Thus, Weiss[10] mentions a case of pityriasis rosea which had continued longer than one year. Graham Little's case of a boy was a recrudescence and not a recurrence, for in this instance the disease lasted five weeks, followed by a month of freedom, then had an acute recurrence for five weeks. Engman and Kile[41] reported a white woman, aged 36 years, with three typical attacks of pityriasis with a minimum period of four years between the attacks. LaRocco[42] reported a 17-year-old boy in whom three attacks of pityriasis rosea occurred at intervals of approximately three or four months, each attack lasting from two to three weeks. Still the eruption disappeared each time after the second roentgen ray treatment with 75 r (unfiltered). This case, too, would fit much better the class of a relapse than of recurrence.

12. *Complications.*—No serious complications follow pityriasis rosea. Reuter[43] has even gone so far as to state, "Complications and sequelae of pityriasis rosea are practically unknown." Reuter, however, did report a thrombophlebitis of the left forearm which developed four weeks after the appearance of a herald spot, no other cause being found. Scratching caused by pruritus, which is usually of moderate severity during the height of the dermatosis, may be followed by eczematization or impetigo contagiosa, or both.

13. *Prognosis.*—Prognosis is good. Involution generally occurs anywhere from four to six weeks. An erythema dose of ultraviolet light from the mercury quartz lamp (Alpine) tends to shorten the course of the disease by several weeks. While mild and even severe constitutional reactions have been reported in pityriasis rosea, the

nervous system has been seldom, if ever, implicated. Jekel[44] reported the case of a 15-year-old white schoolgirl who first became ill with a common cold accompanied by severe headache, which was followed in three days by an eruption on the right side of the trunk. A day later the patient became conscious of a peculiar feeling on the left side of the face with inability to smile and to close the left eye. There was also a disturbance of taste on the left side of the tongue, but no other sensory changes. The patient made a complete recovery from the Bell's palsy in three weeks.

14. *Management.*—Pityriasis rosea is a self-limited disease, the clinical manifestations of which usually subside after four to ten weeks. The remedies that have been employed at one time or other are legion so that no attempt will be made to discuss all of the drugs that have been employed for this purpose. Of particular interest is the injection of milk used by Leiner,[45] a pediatric dermatologist of Vienna, apparently for its nonspecific effect. He reported that in children treated by such injections, desquamation began after four or five days, and involution of the rash began after a week.

Of all methods for treating pityriasis, perhaps ultraviolet light from the mercury vapor quartz lamp is the most useful, and most popular among dermatologists. Hazen,[19] for example, says, "The use of ultra-violet light markedly shortens the course of the disease. It is necessary to effect a very slight erythema in order to cure the disease rapidly. Suberythema doses have little or no effect." Again, Michael[46] says, "In using ultra-violet light in this disease, the effect aimed at is the production of erythema followed by superficial exfoliation. Anything short of this does little good and anything more produces unnecessary temporary disability."

Recently Vass[47] reported on ninety patients treated with highly diluted trichophyton extract 1:500. Treatment was started forty-eight hours after first determining their sensitivity to trichophyton by skin testing. Intradermal injections of the same dilution were given three times weekly in increased doses over a period of two weeks. Itching, if present, stopped after the second or third injection and the eruption disappeared entirely or was only faintly visible after three to six injections. However, 5 per cent of the patients did not show any improvement. In a subsequent study, Vass[48] used fungus extracts (trichophyton and oidiomycin), staphylococcus toxoid, and a sterile solution of lactalbumin in colloidal form as the therapeutic agents with isotonic sodium chloride solution U.S.P. as the control on 270 patients. Good results were obtained with intradermal injections of trichophyton extract "oidiomycin," staphylococcus toxoid (digest modified), and intramuscular injections of a sterile solution of lactalbumin in colloidal form, respectively. No such results were obtained by intradermal injections of isotonic sodium chloride or lactalbumin solution. The theory is expressed that the results were probably due to a nonspecific effect of the active substances. The study did not show any specific evidence in favor of anything of fungus origin for pityriasis rosea. Carpenter, in his comment on Vass's article,[48] suggests that the rapid improvement reported by Vass in patients was due to

daily starch baths and loose clothing, and to a possible nonspecific effect of the trichophyton extract. Carpenter from his previous experience with pityriasis rosea is convinced that pityriasis rosea cannot be considered a fungus infection.

Niles and Klumpp[11] used serum from convalescent patients in doses of 5 c.c. intramuscularly once or twice weekly. While no definite conclusions were drawn, these investigators were encouraged by this treatment, the patients who received serum soon becoming more comfortable, and many stating emphatically that the itching ceased shortly after one injection. Frequently, the inoculation of autoblood (10 c.c.) taken from the patient (median basilic or cephalic vein) and introduced intramuscularly into the buttock has proved quite effective both in relieving the pruritus and in causing the lesions to disappear more rapidly. In the authors' opinion, it has been effective in approximately 40 per cent of patients treated by such means.

The use of soap and water, perhaps because of the alkali contained in the soap, tends to make the dermatosis worse. Accordingly, the use of ordinary soap is contraindicated. Cleansing temporarily may be accomplished by colloidal starch baths or oatmeal baths, which are useful and tend to soothe the highly irritated skin. Klauder[1] states that the liberal use of talcum powder containing menthol and phenol and a daily bath either of starch, bran, or oatmeal water, one pound to thirty gallons of water, are useful. Emulsions and creams are the ideal preparations for topical use. Shake lotions that are drying should be avoided.

The following three case reports are examples of the disease as it occurs in children.

Case 1.—B. S., female Negro child aged 2 years. This child was first seen at the Skin and Cancer Hospital, Philadelphia, by one of us (H. H. P.) on June 22, 1951. The past history is irrelevant. The child, always a healthy infant and bottle fed, had been vaccinated against smallpox but had not received any of the other customary immunologic procedures. The mother stated that the child became ill one week before she was brought to the hospital, and that her complaint was a "sore throat" without fever. On June 16, the mother noticed a few very fine itching "pimples" upon the armpits. At that time she also noticed upon the external genitalia a "ringworm" sore, which grew gradually larger. The rash then spread to the face, head, arms, and body. When the child was first seen at the pediatric dermatologic clinic, the lesions consisted of minute vesiculopapules, especially well marked upon the anterior axillary folds and upon the neck. Other lesions consisted of papules symmetrically situated upon the chest and upon the back. The scalp was characterized by a diffuse folliculitis. Many of the areas of the scalp were covered with thickened crusts (impetigo), as was also the left elbow. A thickened, crusted lesion (eczematized) was seen over the right labia majora; it apparently marked the site of the herald patch. Later the rash became papular with many scaly macules. Conservative treatment by means of starch baths and a one-half per cent liquor carbonis detergens in calamine emulsion gave relief from itching.

Interesting was the examination of the mucous membrane of the mouth at the time the child was first seen. Numerous small vesicles surrounded by an erythematous halo were seen upon the buccal mucosa and upon the mucous membranes of the hard and soft palates. A blood Wassermann was reported negative. A biopsy, tak-

Fig. 1 (Case 1).—B. S., Negro female, aged 2 years, with vesiculopapular and papular lesions of pityriasis rosea. The papules and some macules follow the cleavage lines of the ribs. The herald patch upon the right labia majora has become eczematized through scratching. Note that the thighs are practically free from the rash.

en June 28, 1951, was reported as follows: Degeneration of the lining epithelium, slight capillary hyperplasia, lymphocytic infiltration, granulation tissue, fibrosis. Diagnosis: mild, nonspecific dermatitis, compatible with pityriasis rosea. This child made an eventual recovery. The body was entirely clear of the rash five weeks after she was first seen.

CASE 2.—H. J. L., white female aged 6 years 11 months. This child was first seen by one of us (H. H. P.) on Feb. 24, 1951, because of a generalized pruritic eruption mostly upon the chest, abdomen, and back, of approximately one month's duration. Past history: a full-term healthy baby, delivered normally, birth weight 8 pounds, 9 ounces. Breast fed until six months, she throve nicely. Development was normal; a brother in good health. The patient had had the usual immunologic procedures during infancy, having been successfully vaccinated against smallpox after the first two vaccinations upon the arm failed to "take." On Feb. 1, 1951, a circinate lesion about the size of a quarter piece appeared upon the skin overlying the left shoulder blade to which the mother paid little attention. On February 12, a faint rash appeared over the patient's chest and back which rapidly became generalized and resembled prickly heat. This rash also came to involve the skin behind each ear lobe, although the face remained free of any rash. There was no elevation of temperature. The child continued at school, felt in perfect good health, made no complaint of feeling tired, or of having a "sore throat."

Fig. 2 (Case 1).—Histopathologic section taken from the skin of the left shoulder. Note the large number of vesicles (indicated by the arrow) in the rete malpighii and in the upper portion of the epidermis just beneath the stratum corneum. Note also the presence of a degree of parakeratosis in the stratum corneum above and to the right of the vesicles, acanthosis and the extreme pale-staining effect of the entire epidermis (edema).

The family physician being consulted called the condition "measles." The child was put to bed, given a "shot" of 300,000 units of procaine penicillin in oil intramuscularly; penicillin per os was also prescribed. The rash spread during the following two days to involve the skin of the abdomen and the entire back of the chest and lumbar regions. Still, except for slight itching, there was no discomfort. The attending physician, called in again, in the absence of bronchitis

or running nose, insisted that the condition was "measles." Accordingly, a second "shot" of procaine penicillin in oil, 300,000 units, was administered intramuscularly on February 16. At this time penicillin was discontinued orally and Chloromycetin capsules ordered. A liquid antihistaminic to be taken every four hours was also prescribed to be taken at the same time as the Chloromycetin capsules. The rash, still spreading, now involved the neck, face, the scalp, and upper half of both arms. A few discrete "spots" also appeared upon both thighs. The rash had now become very scaly, and the child complained of considerable itching. Yet the temperature remained normal. The following day, when the rash became quite red, more scaly and "angry looking," pediatric dermatologic consultation seemed advisable. On February 24, when the patient was first seen by one of us (H. H. P.), the rash was full blown, consisting of innumerable scaly, macular, oval-shaped and rounded lesions covering the neck, trunk, upper half of the extremities, and less so upon the forearms, ending abruptly at the thighs. The condition was diagnosed as macular lesions of pityriasis rosea. The course of the disease was uneventful. In another

A. *B.*

Fig. 3 (Case 2).—H. L., white girl, aged 6 years, 11 months. Photographs taken two days after patient was seen (Feb. 26, 1951). The macular type of pityriasis rosea. *A*, Dermatosis at its height ("full blown"). Note the symmetrical, uniform distribution of the macular, scaly, circinate, and oval-shaped lesions which involve mostly the chest, abdomen, and neck. Note how the upper extremities are comparatively free from eruption; also that the lesions upon the lower area of the abdomen, which was the site of later involvement, and upon the chest are more discrete, tending to follow the lines of cleavage, while those situated upon the chest are flatter and more confluent. *B*, Note that the lesions end abruptly at the upper level of the buttocks. The posterior surfaces of both upper extremities are for the most part uninvolved by the rash. The remains of the herald patch can still be seen upon the skin over the left shoulder blade.

week the rash had faded except for a few discrete lesions upon the arms, hands, and legs. Management consisted of starch baths and rose water ointment, containing 2 per cent of salicylic acid.

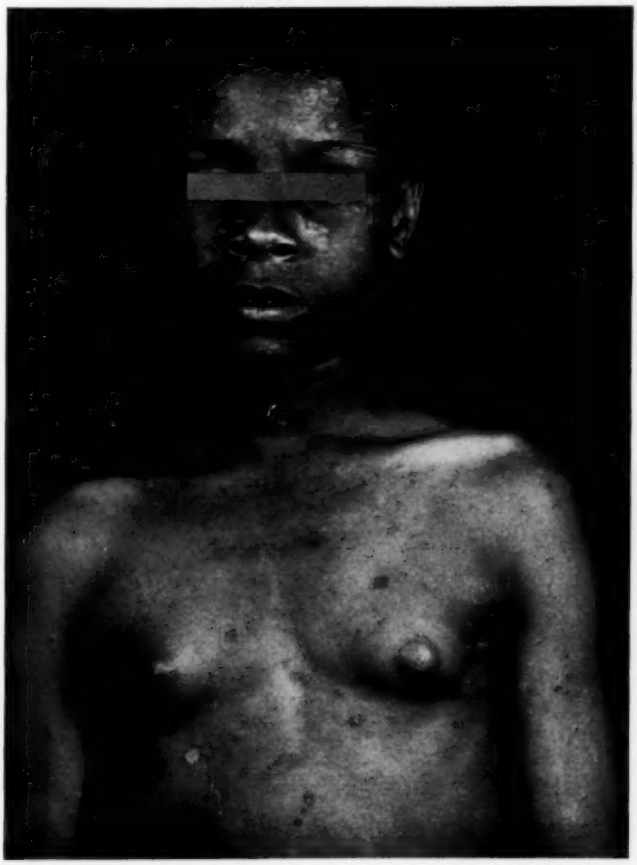

Fig. 4 (Case 3).—C. S., Negro female, aged 8 years. Papulofollicular type of eruption. Note the unusual involvement of the face, the lesser involvement upon the chest and the upper extremities. Interesting is the sparseness of the lesions upon the trunk and extremities compared to those of the face and scalp.

Case 3.—C. S., Negro female, aged 8 years. (This patient was seen by one of us (I. I. L.) on June 28, 1950, at the out-patient dermatologic clinic at the Metropolitan Hospital, with a generalized erythematous, papulofollicular rash. The eruption involved the face, neck, axillae, chest, and upper extremities, and the borderline areas of the scalp. A herald patch, which measured 1½ by 1 inch, was observed upon the anterior surface of the left forearm. This child gave a history of having had repeated attacks of tonsillitis for which she had received sulfathiazole and a gargle containing Dobell's solution. The rash was slightly pruritic. Two weeks later, the lesions had involuted considerably; uneventful recovery followed.

Fig. 5.—Photographs of a case in a Porto Rican girl, aged 11 years, seen at the Flower and Fifth Avenue Hospitals. Two primary lesions which the mother thought were "ringworm" were first noticed upon the left chin two weeks previously. A generalized rash followed approximately one week later involving mostly the trunk, the forearms, arms, and the thighs. This patient complained of considerable itching of the skin. There were no constitutional symptoms. When the patient was seen one week later, the lesions upon the trunk were eczematized from scratching. Note the two oval-shaped primary "herald spots" upon the left chin and the characteristic oval and rounded lesions with scales upon the trunk. The lesions upon the trunk follow the cleavage lines of the ribs (early case). (Courtesy Dr. Rafael M. Rivera.)

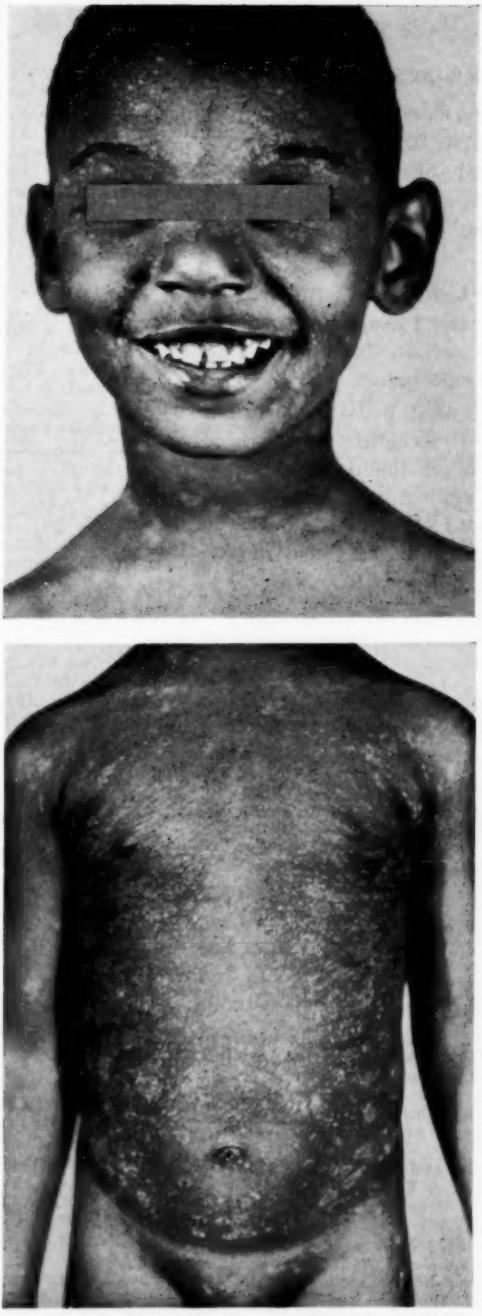

Fig. 6.—Photographs of a case in a Negro boy aged 3 years, 7 months, seen at the Flower and Fifth Avenue Hospitals. This patient demonstrates the "full-blown" clinical appearance of pityriasis rosea, at the height of the dermatosis. Note the oval-shaped scaly macules that cover the skin of the face, neck, and trunk. Many of the lesions upon the anterior trunk are confluent. The rash was first noticed upon the neck three weeks prior to the time the patient was first seen. The herald spot was apparently overlooked. Despite the extensive involvement of the dermatosis, there was very little itching.

SUMMARY

1. The etiology, classification, clinical picture, course, distribution of lesions, differential diagnosis, complications, prognosis, and management of pityriasis rosea in children have been discussed.

2. Several case histories of patients, subjects of pityriasis rosea, including a histopathologic section from a patient, have been reported.

3. It is hoped that pediatricians will be more alert to recognize the clinical manifestations of the dermatosis and will guard against producing a dermatitis venenata (therapeutic dermatitis) from the indiscreet use of topical remedies.

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Psychologic Aspects of Pediatrics

ADOPTION

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ACCURATE figures on the number of adoptions are not available since many adoptions are arranged independently and hence are not recorded. The Mid-Century White House Congress estimated that almost 38,000 children were adopted by people unrelated to them by birth or marriage in 1948. An equal number were adopted by relatives.

The number of adoptions is increasing. According to the report of the New York State Citizen's Committee of One Hundred for Children and Youth (1951) there were two and one-half times as many legal adoptions in 1949 as in 1940.

Adoption of children by people not related to them is accomplished through social agencies or by independent arrangements. Amatruda and Baldwin found that 76 per cent of agency placements were "good" compared to only 46 per cent of independent placements. The criterion for a good adoption was the placement of a healthy, normally intelligent baby in a stable, secure home where a decent upbringing could be expected. Their study, based on 200 cases, gives definite evidence of the superiority of agency placement.

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The disadvantages in agency placement are (1) the babies are older when first placed, only fourteen being under 3 months of age as compared with seventy-nine independently adopted in Amatruda and Baldwin's series. All were not placed until 2 years old while all of the independent placements were made before 1 year of age. (2) The agencies do not handle enough adoptions and are too slow in making the arrangements.

There are always risks in adoption although a probationary period decreases these. No mechanism exists for removing an adopted child from an undesirable home except for physical abuse or neglect, nor for removing a baby who is a poor adoption risk from good parents.

WHY COUPLES ADOPT A CHILD

Generally speaking, parents adopt a child because they are unable to have one of their own. An exception is the child of a dead or destitute relative or friend. Sterility is the most common cause of childlessness. It is often organic but it may be functional. The generative organs of both partners seem to be entirely normal and no contraceptive measures are used, yet conception does not take place. In such cases, the mother often becomes preg-

nant after adopting a child although previous attempts were fruitless. The mechanism of functional sterility is not understood. It is regarded by some as representing an unconscious avoidance of conception by the woman on the basis of a dislike of children. Whatever the mechanism, experience shows that, by and large, these women make very good mothers.

Most couples who adopt a child greatly desire one. Occasionally the reason for adoption is fear of a hereditary taint like insanity or amaurotic family idiocy or because of a previous experience with a defective child. Children are not infrequently adopted in an effort to preserve a shaky marriage. As might be expected the procedure under such circumstances is only rarely successful. Sometimes a sense of duty to society or the prestige value of having children is the principal incentive. Occasionally, in farm communities especially, a child is adopted as a source of cheap labor.

TRUE MOTHER'S ATTITUDE TOWARD ADOPTION

It is hard for a mother to give up her child. If she appears to be in a hurry to be rid of him or has decided during pregnancy to have him adopted she is most probably voicing the opinion of others or she is being pressed by relatives. In such instances the maternal attitude often changes after the delivery.

The decision to give up a baby is likely to be permanent if it is based on sound thinking and planning. Factors to consider are the mother's attitude toward her illegitimate child, her ability to care for him, the effect of the child on her family, and her plans for the future.

Many mothers feel they can make a better decision if they are separated from the child. In such instances foster care for the infant can be arranged. It usually takes a mother three to six months to decide to give up her child permanently. Many agencies do not permit first adoption papers to be taken before six months.

In New York City many infants who are to be adopted are taken from the hospital at 5 to 10 days of age and kept in study homes until they are old enough to have developmental tests—about 12 weeks. The homes are, for the most part, well run and the infants get plenty of mothering.

PARENTAL ATTITUDES

Adoptive parents are usually older than true parents since they have tried for some years to have a child of their own and then have had to wait until a suitable infant became available. Like most older parents they tend to be overaffectionate, overanxious, overprotective and overindulgent. In addition, their self-confidence has been to some extent undermined by their inability to propagate and they consequently feel inadequate.

A certain proportion of adoptive parents are rejectors. This is to be suspected when the decision to adopt a child has been unduly prolonged or when excessively rigid specifications are set up for the type of child to be taken. The search for a child with specific attributes such as blond hair, blue eyes, and so on may be determined by their having had such a child of their own and lost him, but more often it is indicative of a certain aversion toward children. Such persons are likely to be fixed on the desired sex of the child. They often prefer an

older child since they regard little babies as bothersome and messy. On the whole the best foster parents are those who are unable to have a child of their own because of organic sterility.

Some adoptive parents are concerned that the child may have inherited undesirable traits and they fear, when the true parents are unmarried, that the child will lack sex control. Such fear is baseless. The child of an illicit union is just as susceptible to training as are other children. Misbehavior cannot be blamed on the unknown background.

Though most communities require that the adopted child and the adoptee parents are of the same religious faith, occasional inter-faith adoptions take place. These may give rise to serious difficulties later on and should not be encouraged.

CHILD'S ATTITUDE TOWARD BEING ADOPTED

Most adopted children grow up with quite normal feelings and attitudes toward the parents. Even when the adoptive parents have their own children, the adopted child is generally accepted fully. Intrafamilial harmony is threatened when the parents fail to inform the child of his status and he discovers it in an emotionally disturbing way; and when the parents, out of a mistaken notion that any deviation in the child's behavior is due to his bad heredity, proceed to introduce strenuous remedial or disciplinary measures. The parents fail to realize that, from time to time, every normal child behaves in an irritating and annoying way and even engages in behavior which may be alarming.

EARLY VERSUS LATE ADOPTION

When a child is adopted during infancy he has the advantage that his adoptive home is the only one he has ever known and the adoptive parents are the first ones to whom he makes emotional attachments. There has been no opportunity for previous bad handling. When a child is adopted at a later age he will resent the change of domicile even though his previous home may have been much inferior to his new one. A child of only 3 or 4 years is acutely aware of the change. Sometimes the child is unaccustomed to the attention of affectionate parents and hence does not know how to respond. If he has been adopted from his own home there may be resentment at being taken from his family, and shame that his parents would give him up.

A child who has been in an institution for an extended period before adoption may show the undesirable personality traits which result from emotional deprivation thus making management by the adoptive parents difficult. Shifting from one foster home to another is also disturbing. On the other hand, if the child has been reared in a foster home or in an institution where the attendants were warm and affectionate, there will be no undesirable effect on his personality development. Many of these children have made good adjustments in later life. Fortunately most placement agencies understand the nature of the trauma which may result from separation from the mother and residence in an institution.

Obviously none of these objections holds when a very young baby is adopted. Here, however, the risk of undetectable abnormalities is greater, the uncertainties of developmental de-

viations are ever present, and the intellectual potentialities are undeterminable with any exactness.

In general the best advice is for the prospective parents to select a baby within the first six months of life whose background has been carefully investigated and whose physical examination, and Wassermann and tuberculin tests reveal no abnormalities.

INFORMING THE CHILD

Most 2- and 3-year-old children are probably aware, at the time, of the change to a new home but they quickly forget. The older they are at the time of adoption the more clearly do they comprehend their changed status.

Parents should inform the child that he is adopted as soon as he is old enough to comprehend—usually during the fourth year. At first he will understand little and promptly forget what he has been told but as comprehension grows and the information is repeated he will come little by little to grasp the situation. Not to tell the child may expose him to an uncomfortable and even distressing situation since sooner or later the information will come to him from playmates or bits of overheard conversation. Fear that the child has discovered his true status and is brooding over it is a common source of worry among parents who have not told the child that he is adopted. The adoptive parents may put off informing the child because they are eager for him to have the "security" of growing up in the belief that they are his true parents, or they may be merely postponing a task which they find difficult and somewhat distasteful.

The information is best given to a 3- or 4-year-old child as a story about a mummy and daddy who had no children of their own and who looked everywhere until they found a baby who just suited them. And that is the way they got him.*

The child should never be reminded that he is adopted when the parent is angry or otherwise displeased with him. He should know that he was deliberately chosen, that his present home is permanent, and that he is very much wanted.

When he is old enough he should be told something about his true parents. They should be presented in the most favorable light possible, as the victims of accident or misfortune so that no blame may be attached to them. When nothing is known about the parents the child may gain assurance by receiving information about his nationality and the stock from which he has sprung. It is not advisable to have the adoptive parents meet the true parents. The child should not be told the name of his true parents nor their whereabouts. It is best for him to understand that they are dead.

CHILD'S CONCERN ABOUT BEING ADOPTED

It is helpful for the parents to know that, at certain periods in their child's life, he will be especially concerned about being adopted. If they can anticipate his questions and reactions they will be prepared to answer them and they will be less likely to become confused and anxious. The child's reaction to being adopted is, to a large extent, a reflection of that of his parents. If their attitude toward him is one of affection and understanding, he will react similarly to them and he will feel safe and confident in his relations

*See Wasson, V. P.: The Chosen Baby, Revised Edition, New York, 1950, J. B. Lippincott Company.

with them and consequently his doubts will be easily resolved.

The first period of questioning comes when the child begins to go to school and to have new experiences outside the home. At this time even true children not infrequently think that they are adopted. Sometimes, when they consider that they have been punished or deprived unfairly, they react with the feeling that their own parents could not possibly be so unkind to them and such expressions as: "You aren't my real mother. I hate you," are not uncommon. Even true mothers are hurt by these outbursts, but the adoptive mother is likely to feel guilty and to wonder whether she is bringing up her child properly. If the parents are prepared for these reactions and expect them, the rage episodes will not be so disturbing to them.

The second period is during adolescence when the desire to be like other children is very strong and when being adopted means being different. However, other interests, such as being included in a group and having many dates, are more important at this age and the worry is not deep-seated.

The third period is during late adolescence when concern about true family background and heredity is on a more mature level. New doubts arise in the adolescent's mind: Will he ever marry, what will his mate think of his being adopted, what will his children inherit? Having some information about his background and family will help to answer these questions. The knowledge that they were of a certain socioeconomic group and national background, that their occupations were of a certain kind are helpful. An appreciation that attitudes, skills, and behavior patterns are largely learned and not inherent will give assurance.

The fourth period of doubt follows marriage. First, the adopted person is troubled about what his offspring will be like and what unknown, unattractive characteristics may have been inherited. If a child does not conform, the old uncertainties are revived. Peculiarities of appearance, delays in development, difficulties at school arouse doubts. In true families, if the ancestors are known, the discrepancies may be explained and resemblances to relatives discovered; and when things have turned out well there is reassurance and comfort. With the adopted person an exaggerated significance may be attached to any deviation. Sometimes the mate or his family blame the adopted person for the deviations they do not like.

HANDICAPPED CHILDREN

There are many kindly people who, with full knowledge of the implications of permanent crippling and chronic illness, will gladly adopt a handicapped child. Agencies are beginning to encourage such adoptions. Couples who understand the personal and financial responsibilities which they are assuming should be helped in their noble endeavor.

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News and Notes

The following were certified by the **American Board of Pediatrics** at the examination at Buffalo, N. Y., Oct. 26, 27, and 28, 1951.

Dr. Mathew Blake Arnoult, 1661 Madison Ave., Memphis, Tenn.

Dr. Donald Lou Alexander Bastedo, 230 Frederick St., Kitchener, Ontario, Canada.

Dr. John Edward Baybutt, 214 Dover St., Easton, Md.

Dr. Edmund Charles Burke, Mayo Foundation, Rochester, Minn.

Dr. Charles L. Burr, 409 Equitable Bldg., Des Moines, Iowa.

Dr. Charles Neil Christensen, 421 S. Sixth St., Springfield, Ill.

Dr. James Oliver Cooper, III, 114 West Oak St., El Dorado, Ark.

Dr. Douglas T. Davidson, Jr., 300 Longwood Ave., Boston, Mass.

Dr. Herbert VanDyke Davis, 411 Alameda Rd., Kansas City, Mo.

Dr. Henry Middleton Drinker, 8236 Germantown Ave., Philadelphia 18, Pa.

Dr. Joseph Eiser, 306 N. Soto St., Los Angeles 33, Calif.

Dr. John Denney Farquhar, 4501 Cedar Lane, Drexel Hill, Pa.

Dr. Edward Graham Field, P. O. Box 146, Glen Burnie, Md.

Dr. Irving Fine, 16 Wildwood Ave., San Carlos, Calif.

Dr. John H. Ford, Jr., 25 Schiller St., Binghampton, N. Y.

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Dr. Frederick A. Groff, Jr., 1527 Union St., Schenectady 8, N. Y.

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Dr. Herbert Spencer Harned, Jr., 222 Augur St., Hamden, Conn.

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Dr. Sol Norman Keen, 311 E. 17th St., New York 3, N. Y.

Dr. Charles Kennedy, 3927 Locust St., Philadelphia 4, Pa.

Dr. Sidney R. Kennedy, Jr., 241 Main St., Torrington, Conn.

Dr. Marvin L. Kokomoor, 313 N. W. First St., Gainesville, Fla.

Dr. Jean West Larsen, 18 Orchard St., Middletown, N. Y.

Dr. Bruce William Leppla, 400 South I St., Lompoc, Calif.

Dr. Robert Dawson Lomas, 5101 Fannin St., Houston 4, Texas.

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Dr. Armond Vincent Mascia, 102 S. Broadway, Tarrytown, N. Y.

Dr. Melvin Matlin, 114 Academy St., Poughkeepsie, N. Y.

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Dr. Julia Mehlman, 200 E. 16th St., New York 3, N. Y.

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Dr. Robert W. Monroe, 10 Bentley Ave., Greenville, Pa.

Dr. Francis Newby Mullen, Jr., 412 Medical Arts Bldg., Norfolk, Va.

Dr. Ruth O'Neal, 215 Reynolds Bldg., Winston-Salem, N. C.

Dr. Irving Leonard Samuels, 524 North Ave., New Rochelle, N. Y.

Dr. Jenaro Scarano, 125 Victoria, Ponce, P. R.

Dr. Irving Schulman, Dept. of Pediatrics, New York Hospital, New York 21, N. Y.

Dr. Harrison Clark Spencer, George Ben Johnston Memorial Hospital, Abingdon, Va.

Dr. Edwin Paul Stabins, 3504 Staunton Ave., S. E., Charleston, W. Va.

Dr. Ruth Esther Standard, Germantown Dispensary Hospital, Germantown, Pa.

Dr. Felix Stein, 575 Ocean Ave., Brooklyn 26, N. Y.

Dr. S. David Sternberg, 1433 Union St., Brooklyn 13, N. Y.

Dr. Daniel Stowens, Capt. (MC) 6014th ASU, U.S. Army Hospital, Camp Cooke, Calif.

Dr. Albert William Sullivan, Strong Memorial Hospital, Rochester, N. Y.

Dr. Robert F. Sylvester, Jr., 1385 Grandview Ave., Columbus, Ohio.

Dr. Frank L. Tabrah, 507-509 Herald Bldg., Bellingham, Wash.

Dr. Victor Clarence Vaughan, III, 789 Howard Ave., New Haven, Conn.

Dr. William J. Waters, 705 State Tower Bldg., Syracuse, N. Y.

Dr. Samuel Swartz Woolington, 541 E. Broadway, Long Beach 2, Calif.

Dr. John Harvey Zimmerman, 10 E. Fourth Street, Greensburg, Pa.

Dr. Ching-feng Hsu, Queen Mary Hospital, Hong Kong, China.

Dr. Hassen Ahari, 67 Jalleh Ave., Teheran, Iran.

The **American Board of Pediatrics** has changed the date of the oral examination previously announced to be held in St. Louis in April, 1952, to March 21, 22, and 23, 1952.

Dr. F. Howell Wright has been promoted to a full professorship of pediatrics at the University of Chicago Medical School.

Dr. Norman Gregg of Sydney, Australia, has been awarded the Mickle Prize of the University of Toronto for outstanding work in "world medical research." Dr. Gregg was the ophthalmologist who in 1941 recognized the relationship between rubella in the early months of pregnancy and congenital cataracts in the newborn infant.

The central theme of this year's regular refresher course for pediatricians at **Tulane**, Feb. 11 through 16, 1952, inclusive, will be "Accidents." Visiting faculty members for the course will include Dr. George Wheatley of New York City, Dr. Albert D. Kaiser of Rochester, N. Y., and Dr. Irvin Kerlan of Washington, D. C. Major emphasis will be paid to defining the pediatrician's role in community planning for prevention and management. Those interested should communicate directly with the Department of Pediatrics or the Division of Graduate Medicine, Tulane Medical School, 1430 Tulane Ave., New Orleans, La.

According to the November reports of the U. S. Public Health Service, there is an increase over last year in the number of cases of measles being reported. The increase is chiefly in the New England and Middle Atlantic states.

Book Reviews

Handbook of Pediatric Medical Emergencies. Adolph G. DeSanctis, M.D., and Charles Varga, M.D., St. Louis, 1951, The C. V. Mosby Co., 284 pages. Price $5.00.

This is a useful and practical text that should be in the receiving room of every hospital in the country. Pediatricians will find it an important addition to the permanent shelf of their library. The *Handbook* is an outgrowth of material prepared over a number of years by Dr. DeSanctis and his staff for postgraduate students and a few years ago was privately published in a booklet of 90 pages. This revised text, greatly enlarged over the earlier booklet, resulted from the demand for the privately printed edition.

The first five chapters discuss the treatment of medical emergencies of the cardiovascular, gastrointestinal, genitourinary, central nervous, and respiratory systems. As a rule, the authors give only the method of treatment for the emergency that they have found best in their own experience, and do not discuss the variations in use in other clinics which are usually of minor importance. The material is thus based on experience rather than a compilation. Chapter 5 discusses drowning and describes the Eve method of artificial respiration used in Great Britain, as well as the Schäfer method usually taught in the United States.

In some ways the chapter on accidental poisoning is the most useful in the book. These are emergencies which call for immediate treatment. They comprise some 1 per cent of pediatric hospital admissions and are responsible for the deaths of many children each year. In the chapter in the text the treatment is given for the active poisonous agent or drug. To this the authors have added an appendix listing the poisonous substance in over 500 commercial preparations which may be the cause of the poisoning, as so and so's ant paste, roach killer, rat poison, weed spray, cough medicine, etc. Anyone who has had the experience of having to telephone half way across the country to some manufacturer to find the formula of some preparation which has been accidentally ingested by a child will appreciate the value of this list. We are certain that the authors would appreciate additions to this list based

on the experiences of pediatricians in all parts of the country.

Miscellaneous emergencies as bites, burns, and hiccough are considered in another chapter. A new section not appearing in the earlier booklet is an excellently illustrated section on pediatric procedures as vein puncture and lumbar puncture. From this review of the contents and character of the *Handbook*, it is obvious why it is so valuable for immediate reference and use when a pediatric emergency occurs. It makes readily available so much that the pediatrician or younger house officer cannot be expected to carry in his head, and yet may be the important factor in saving the life of the child.

Angiocardiography as a Diagnostic Aid in Congenital Heart Disease. J. W. C. de Groot, M.D., Amsterdam, 1951, Keesing, 108 pages.

This monograph is divided into two parts.

Part I: This section is devoted primarily to a historical survey of the literature on angiocardiography. The various methods and techniques used by various workers in this field are described together with the complications that have resulted. The various indications and contraindications are specified and a general discussion of normal and abnormal angiocardiographs is given.

This section is of value as a general explanation of method and procedure.

Part II: This section gives a very brief description of the bare techniques used by the author in performing a series of fifty-one angiocardiographs on patients with various types of cardiac abnormalities. The remainder of this section describes the findings in various specific types of abnormalities, such as tetralogy of Fallot, tricuspid atresia, transposition of the great vessels, etc. Under each heading, several specific cases are cited with a short résumé of the clinical history and findings, and a more detailed account of the angiocardiographic findings, with a full discussion and explanation of these findings.

The running text is not accompanied by diagrams or illustrations, but there are nineteen illustrations at the end of this section, given to illustrate specific abnormalities.

In general, the monograph is well done and easily readable. It will be of value in correlating the angiocardiographic findings with the other findings of patients with these types of cardiac abnormalities.

It would seem that its value would be enhanced had it been possible to more profusely illustrate the running text with diagrams and pictures to more clearly illustrate the points discussed. CARSON.

Medicina Infantil. Juan P. Garrahan, Buenos Aires, 1951, "El Ateneo," ed. 7 (corrected and enlarged). 1,196 pages, 197 illustrations; also 21 full-page plates in black and white, and in color; with an index. Price, paper bound 160, imitation leather 180 Argentine pesos (approximately $21 and $24, respectively).

The seventh edition of Garrahan's textbook, long and justifiably popular among Spanish-American physicians, represents a genuinely solid accomplishment.

The volume is divided into three sections. The first, numbering 468 pages, is devoted to the physiology and diseases of infants; the second, 616 pages in length, concerns disorders which occur in both infants and children; the final section deals with miscellaneous matters peculiar to pediatrics.

While the book manifests some of the shortcomings which inescapably result from single authorship, the discussion of most topics is authoritative, objective, and well documented. Bibliographic references, while numerous, are not nearly so complete as one might wish and are somewhat inconveniently inserted into the text, whence they cannot be retrieved without search. There are some significant omissions, of which systematic treatment of growth and development, pediatric urology, disorders of the skeleton and of the emotional problems of childhood may be mentioned. As in many medical textbooks, the quality of reproduction of photographs and x-rays leaves much to be desired.

These criticisms are not intended to be derogatory: the book as a whole is good. In fact, it is, from the point of view of this reviewer, probably the best and certainly the most up-to-date textbook of pediatrics in the Spanish language available today.

D. J. McC.

Physiology of the Newborn Infant. Second edition. Clement A. Smith, M.D., Springfield, Ill., 1951, Charles C Thomas, 348 pages. Price $7.50.

The second edition of Smith's *Physiology of the Newborn Infant* has been completely revised and rewritten and contains many dis-

cussions in the text to work that has appeared since the first edition in 1945, as, for example, the studies of Barcroft and of J. L. Wilson. It is a field in which there are many gaps of knowledge and new studies are constantly being reported. Dr. Smith has maintained the same critical viewpoint to the new that he so well held in the first edition. The care of the infant is still and will continue to be the basis of pediatric practice and a knowledge of the physiology of the newborn infant is fundamental to the work of the pediatrician. The first edition in 1945 was an outstanding contribution to pediatrics which deservedly won a "must" place on the pediatrician's book shelf. This second edition not only brings into relationship the newer work, but the revision has given Dr. Smith the opportunity of improving and clarifying the discussion in the earlier text. He has taken advantage of the opportunity in an admirable way and the second edition is a better book.

Maternal Nutrition and Child Health. Bulletin of the National Research Council No. 123, Washington 25, D. C., 1951, National Academy of Sciences, 174 pages. Price $2.00.

This is the third report by the Committee on Maternal and Child Feeding of the Food and Nutrition Board of the National Research Council. The basis of the report was prepared by the late Dr. Kirsten Utheim Toverud, of Oslo, whose work in the field of maternal and child health and nutrition is internationally known. Dr. Toverud spent six months in this country in 1948 working on the report, and after her death the material was put in its final form by Genevieve Stearns and Icie G. Macy.

The first chapter is a well-selected study of maternal and infant mortality statistics, and shows the tremendous progress that has been made in lowering mortality rates. The second chapter takes up the question of specific nutritional factors in maternal and child health. All of the various food substances, as proteins, minerals, and vitamins, are considered in detail and the present-day knowledge of the part each plays is discussed. A third chapter discusses the importance of prematernal, prenatal, and postnatal care. An extensive bibliography contains references to over a thousand studies and reports referred to in the text. The bulletin gives a complete picture of the present status of our knowledge of nutrition as it affects maternal and child health, and will be of great value and help as a reference text to the many workers in these fields.

Eating Problems for Children, a Guide for Parents. 17 pages.

Eating Problems for Children, a Guide for Doctors and Nurses. 17 pages. Published by the National Association for Mental Health, 1790 Broadway, New York 19.

These are pamphlets on eating habits and problems. While there is nothing new they both contain fairly sound material to be placed in the hands of parents and nurses. Many pediatricians will disagree with some of the advice, as, for example, making the holes in the nipple so small that the baby will have to take twenty minutes to empty the bottle. The purpose is to meet the psychologists' ideas of satisfying the "sucking" desires and needs of the infant. This advice hardly fits in with the well-known fact that a normal happy thriving breast-fed infant takes over 90 per cent of its breast feeding in the first five minutes of nursing. One can picture the frustration and complaint of a hungry baby who receives but a trickle from the bottle. Many will regard it as too much psychology with a disregard of practical experience and a knowledge of infant feeding. It is difficult to understand how a definite twenty minutes for the bottle fits in with the avoidance of rigidity of schedule emphasized in other parts of the pamphlet. The reviewer is puzzled why the word "doctors" was added to the second pamphlet. While it may have value in creating attitudes on the part of nurses, it is entirely too superficial for doctors. The material is chiefly based on the work of the Aldrichs, Spock, Davis, and others whose detailed studies are well known to doctors. The pamphlets may be obtained from the Association at 15 cents each, with reductions for quantity lots.

Editor's Column

TRENDS IN PEDIATRIC EDUCATION

DURING the past year the Committee on Medical Education of the American Academy of Pediatrics has held ten regional conferences on pediatric education. Regions were so divided that in each region there were from six to ten medical schools with the exception of Region X, which included all of the Canadian medical schools. Each member of the Committee served as a "Captain" for his region. Invited participants were the heads of pediatric departments or their representatives from the medical schools in the region, state and district chairmen, and other guests at the discretion of the "Captain." Purposely, no common agenda was supplied the conferences in the belief that the problems in the regions would differ widely and that there would be value in a later comparison of the approach made to these problems in the different conferences. Summary reports of all the conferences have been brought together and will be distributed to the participants, but will not be published elsewhere. The purpose of this editorial is to provide the readers of the JOURNAL with a brief "summary of the summaries."

In addition to the conferences, the Committee sponsored an exhibit and a panel discussion on pediatric education for the annual meeting of the Academy at Toronto. It will be recalled that one of the major findings to emerge from the nationwide Study of Child Services was the fact that some 75 per cent of the nation's children receive their medical care from general practitioners, an additional 14 per cent from specialists other than pediatricians, and the remainder from pediatricians. At the same time it became clear from the survey of the pediatric departments in the seventy-odd medical schools of the country, that there was wide variation in the quality and quantity of pediatric education being dispensed at the undergraduate level. It seemed logical, therefore, to conclude that one of the most effective approaches to improving the health of children on a national scale would be to improve pediatric education in every way possible. It is toward this objective that the Committee on Medical Education is directing its efforts.

As one studies the summary reports from the different conferences, it is clear that the educators have two broad objectives in mind. One is to do a better job of teaching pediatrics in the medical schools so that the students who will later become general practitioners with little or no further training in pediatrics will be better equipped to provide medical care to their child patients. The other is so to design the pediatric curriculum that it meets the needs of private practice with its shifted emphasis from treatment of disease to the broad aspects of prevention.

Only a few of the numerous topics which came up for discussion in the various conferences can be cited here to illustrate the trends which pediatric education is taking. The following have been selected for this purpose.

1. The basic function of a department of pediatrics was defined as concerned primarily with clinical teaching, research, and service. Organiza-

tion should be such that none overshadows the others, and all three are developed to their optimum. The first two years of the pediatric resident's specialized training should be along the broad principles of fundamental pediatrics and should not be diluted by excessive time spent on isolated research.

2. In none of the conferences was there a formal recommendation for the establishment of minimum or optimum standards which should be met by all pediatric departments. Nevertheless, because of the wide variations found in the original survey among pediatric curricula in such items as total hours allotted to pediatrics, number of full-time staff, instructors per student, in- and out-patients per student, etc., it was felt that some consideration might well be given to what should constitute optimum practice. It is the intention of the Committee to make some headway in this direction in next year's conferences.

3. The evaluation or score sheet used by Dr. Mitchell in the original survey of pediatric departments was most useful for that purpose. It consists of twenty-eight separate items, each of which contributes to the organization and effectiveness of a pediatric department. Each item is assigned a numerical grade ranging from a top figure to zero. It was agreed in all conferences that it was impractical and undesirable to carry out formal re-evaluation of pediatric departments on a yearly basis. Nevertheless it was felt that the score sheet could be very useful to individual departments which might wish to check on their own status. It is proposed to revise the evaluation schedule from year to year according to suggestions arising from the conferences.

4. All conferences spent considerable time discussing methods of teaching pediatrics in the medical school. One of the most interesting developments is the trend away from the didactic lecture, and toward teaching around the patient. In some schools, the didactic lecture has been almost completely abandoned, in others the hours have been drastically curtailed. The opinion of the majority seems to be that teaching which arises from the observation of and responsibility for a specific patient constitutes the most valuable type of teaching. It should be added, however, that there were many who favored retaining a minimum number of lecture hours, illustrated when possible by audiovisual aids, to present material which the student might not encounter or which he might have difficulty finding or understanding in textbooks.

Advantages of out-patient teaching were especially stressed. It was recommended that at least an equal amount of time to that devoted to in-patient or bedside teaching be devoted to out-patient teaching. The out-patient simulates more closely private practice, and provides a better opportunity to teach the problems concerned with the welfare of the "whole child" in contrast to in-patient teaching which emphasizes a disease or an organ.

5. Closely related to the trend toward curtailing the didactic lecture in favor of teaching around the patient is the movement to minimize isolated departmental teaching in favor of horizontal and vertical integration between all departments. Basic sciences have many tie-ins with clin-

ical pediatrics where correlated teaching would be most helpful to the student. In the clinical years, for example, the surgeon, the roentgenologist, the pediatrician, the biochemist, the psychiatrist, the geneticist may all combine to give the student a thorough understanding of the total impact a disease may have upon the patient and upon his family—a concept not easily obtained department by department. Breaking down of interdepartmental barriers may be difficult among long-established strongly entrenched departments.

6. Teaching of growth and development, public health, and well-child care is assuming increasing importance in the undergraduate curriculum in view of the changing emphasis in pediatric practice from physical illness to prevention. Their integration into the teaching program is not as complete in some schools as seems desirable. Growth and development is basic to pediatrics and embraces the essential differences between pediatrics and adult medicine. In Colorado, Dr. Washburn has organized a course called "Human Biology" for first-year students. It consists of weekly lectures and seminars with periodic demonstrations of the dynamics of growth.

7. Particularly important to the training of the general practitioner are the problems of the newborn and the premature infants. Teaching in this field is handicapped by reluctance to permit the student to visit the nursery to examine babies. In the conference of Region I, Dr. Stewart Clifford described in detail the teaching of these subjects in current use at the Harvard Medical School.

8. Several innovations are being tried out in various medical schools in an effort to give the student a better orientation concerning private practice. "Farming-out" of third- or fourth-year medical students to general practitioners in small communities for brief periods was reported upon favorably in one of the conferences. The principle of assigning a specific family to a freshman medical student whose fortunes, good or bad, he will follow throughout his medical course was felt to have merit and to be worthy of further exploration.

Space does not permit recording here the numerous other subjects discussed at the regional conferences. But perhaps these which have been documented will be sufficient to permit the reader to gain an insight into what the educators are talking about, and also to give him an idea of the value the conferences may have in bringing together educators and practitioners to "pool" their ideas and to discuss their problems.

L. F. H.

IRON POISONING

NEARLY two years ago in the March, 1950, issue, the JOURNAL commented editorially on the danger of acute poisoning in young children from the accidental ingestion of large quantities of medicinal iron.[1] The editorial was based on four fatal cases reported in the British literature.[2, 3] It further noted that the possibility of medicinal iron being a potential cause of severe and even fatal poisoning was not mentioned in any of the standard pediatric texts.

A few weeks ago two manuscripts were submitted to the JOURNAL within a twenty-four-hour period reporting four cases of poisoning in young chil-

dren from the accidental ingestion of ferrous sulfate tablets. In two of the cases death occurred. This unusual circumstance prompted a study of the literature since the earlier British reports to find if other cases had been reported. Thompson,[4] who reported two fatal cases in 1947, added four cases in 1950. One of these was fatal and was described in detail by Prain in 1949.[5] Lindquist[6] in 1949 reported a nonfatal case in Sweden from the ingestion of ferric chloride tablets and mentioned a nonfatal case of Magnussen's which has not been reported in detail.[7] In the United States, Smith and associates[8] in 1950 reported the history and autopsy findings in a child of 17 months who had ingested ferrous sulfate tablets, and Murphy and collaborators[9] a nonfatal case in a 30-month-old child.

With the addition of the one fatal and two nonfatal cases of Duffy and Diehl,[10] and the fatal case of Swift, Cefalu, and Rubell,[11] reported in this issue (pp. 1 and 6), we find that eight fatal and eight nonfatal cases of accidental poisoning in young children from the ingestion of medicinal iron have been reported since 1947. It is difficult to determine from the reports the actual amount of iron ingested in these cases, as usually the number of tablets taken is uncertain, and, further, as violent vomiting is a prominent and early symptom, an indefinite number of tablets have been eliminated in the vomitus. Symptomatically, bloody vomiting followed by shock usually develops within an hour or so after the ingestion of the tablets. Pathologically, hemorrhage from and necrosis of the gastric and intestinal mucosa are found. Death has occurred in the fatal cases in from four to forty hours after the tablets were ingested. The youngest child in the series was 11 months of age, and most of the cases occurred in the 18- to 30-month age group.

It is puzzling to understand why medicinal iron preparations, which have been used therapeutically for many generations and which have been looked upon as almost innocuous in overdosage according to the medical texts, should first be reported in the last few years as a cause of severe and fatal accidental poisoning in young children. It is obvious that the potential danger of medicinal iron as a cause of accidental poisoning should be better known to physicians and the public, and that when they are prescribed, the physician should warn patients and parents that death has followed their ingestion in quantity by young children. This is of increasing importance in view of the practice of a number of the "blood banks" established in the last few years giving the donor an envelope containing ferrous sulfate tablets to be taken over a period of a few weeks following the donation. Perhaps most important is the closing line of the previous editorial which was italicized:

"Iron preparations should be kept out of the reach of infants and young children."

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